UNIVERSIDADE DE LISBOA

FACULDADE DE PSICOLOGIA

EXPERIENCES OF FAMILIES LIVING WITH CONGENITAL DISORDERS OF GLYCOSYLATION A QUALITATIVE STUDY

Carolina Lopes Cardão

MESTRADO INTEGRADO EM PSICOLOGIA

(Secção de Psicologia Clínica e da Saúde / Núcleo de Psicologia da Saúde e da Doença)

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Dissertação orientada pela Professora Doutora Maria Luísa Barros

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2017

Por mais investigação no campo das doenças raras.

Para toda a comunidade CDG.

"That's one small step for a man, one giant leap for mankind."

Neil Armstrong

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RESUMO

Estima-se que a nível global 6 a 8% da população seja afectada por qualquer tipo de doença rara. Uma doença rara não se define apenas pela incidência num grupo pequeno e restrito da população mundial. São doenças complexas, multissistémicas, com impacto físico e/ou cognitivo, muitas vezes genéticas, e não passíveis de se prevenir nem curar, sendo frequentemente letais. Pela sua baixa frequência na população, as doenças raras não são do conhecimento da maioria das pessoas, incluindo profissionais de saúde. Apesar de crescente nos últimos tempos, a investigação no campo das doenças raras é escassa, justificando em grande parte a falta de conhecimento demonstrado pela comunidade médica e científica, o que acaba por afectar directamente os pacientes, os seus familiares e os seus cuidadores. Nos últimos tempos tem-se assistido, no entanto, a uma consciência crescente do impacto que as doenças raras têm nos vários contextos. Tem-se também verificado um maior investimento no desenvolvimento de técnicas de diagnóstico, em medidas de cuidados de saúde e em projectos de investigação nesta área. Isto deve ser valorizado, pois mesmo partilhando muitos dos impactos mais gerais e comuns das doenças crónicas, as doenças raras têm dificuldades específicas subjacentes. Embora os diferentes tipos de doenças raras tenham as suas especificidades e afectem as famílias de diferentes formas, as necessidades de todas elas parecem ser universais na sua maioria.

Os defeitos congénitos de glicosilação (CDG para o termo *congenital disorders of glycosylation*) pertencem a um grupo de doenças raras e hereditárias. Defeitos totais ou parciais do processo de glicosilação, responsável pela síntese de glicoproteínas, são causas subjacentes a este grupo de doenças. Alterações destes processos biológicos levam a outras alterações do desenvolvimento, crescimento e funcionamento das células O resultado disto reflecte-se nos inúmeros e variados sintomas característicos deste grupo de doenças multisistémicas, maioritariamente físicos e neurológicos Atraso psicomotor, ataxia, epilepsia, estrabismo, implicações imunológicas, cardíacas e hepáticas estão entre os danos mais comuns e característicos dos defeitos congénitos de glicosilação. Tal como na maior parte das doenças raras, o diagnóstico e a ausência de tratamentos efectivos, na maior parte dos tipos desta doença, e de cura são os principais desafios enfrentados pelas famílias e profissionais de saúde. O largo espectro sintomático característico da CDG

reflecte-se nos diagnósticos errados e no tempo prolongado de definição da doença com que as famílias são confrontadas. A maior parte dos tratamentos são sintomáticos.

No presente estudo, procurou-se explorar a experiência vivida pelos familiares cuidadores de pacientes crianças, adolescentes ou adultos portadores de qualquer tipo de CDG. Nomeadamente, procurou-se aprofundar o conhecimento das exigências e mudanças impostas por este grupo de doenças, as principais preocupações e necessidades subjectivas dos familiares, o impacto emocional nestes, os recursos que têm disponíveis e que lhes facilitam a adaptação à vivência da doença, e as estratégias de *coping* mais usadas e úteis para os mesmos.

Para isso, foram feitas entrevistas com familiares cuidadores de pacientes com CDG, recrutados pela Associação Portuguesa de CDG e outras Doenças Metabólicas Raras (APCDG-DMR) que estabeleceu uma parceria de investigação com os autores do presente estudo. Os participantes que mostraram interesse e disponibilidade em colaborar na investigação foram familiares próximos e com contacto frequente com os pacientes (mães, pais, irmãos e avós). Os pacientes foram crianças, adolescentes e adultos, que tinham diferentes sub-tipos da doença em estudo. Antes de realizarem as entrevistas com os investigadores, os participantes receberam um documento explicativo dos objectivos do estudo e um consentimento informado para assinarem e enviarem antes de ser agendado o dia e a hora da entrevista. A amostra caracterizada por 40 participantes de diferentes países justificou a realização das entrevistas *online*, recorrendo ao *software* Skype™ - Version 7.36.0.101 (Skype Communications SARL). As entrevistas foram conduzidas por um guião de entrevista semi-estructurada, elaborado no início da investigação. Posteriormente, o conteúdo das entrevistas foi transcrito, traduzido para a língua inglesa e analisado, recorrendo a uma análise qualitativa temática e exploratória auxiliada pelo *software* Nvivo 11 Pro for Windows.

Da análise e codificação das entrevistas surgiram nós, que se agruparam posteriormente em sub-categorias e categorias, dando origem no final a três grandes dimensões representativas da experiência vivida pelos participantes – *Diagnosis*, *Living with CDG* e *Messages for other families* – segundo os seus relatos. Apesar das diferenças individuais, influenciadas por variáveis socio-demográficas, os relatos dos participantes foram maioritariamente semelhantes.

Foi possível identificar os principais factores associados às exigências do papel de cuidador e ao impacto psicológico sentido, e as principais estratégias de *coping* usadas para lidar com os desafios físicos e emocionais diários derivados da doença.

Cuidar de um paciente CDG mostrou ter nos participantes impactos ao nível físico e emocional. A presença de emoções negativas e a dificuldade em geri-las inicia-se no momento em que se tem consciência de que algo se passa com o paciente, e mantém-se no dia-a-dia, principalmente quando os familiares cuidadores experienciam situações mais críticas associadas à doença do seu familiar. As preocupações identificadas remetem para o presente e futuro, quer do paciente, como de toda a família e de outros familiares afectados pela experiência vivida com a CDG. Estas preocupações parecem estar relacionadas com as exigências e desafios da doença, nomeadamente aquelas relacionadas com os encargos financeiros dos custos elevados de gestão da doença; com a falta de conhecimento e experiência dos profissionais de saúde no que se refere à CDG, e consequente necessidade sentida pelos cuidadores (principalmente os principais cuidadores, os pais) em assumir as responsabilidades de gestão dos cuidados de saúde do/a seu/sua filho/a; com a dificuldade em aceder a serviços de saúde especializados; com a incerteza da evolução da doença; com o desenvolvimento favorável e bem-estar do paciente, a sua integração social e as suas condições de vida futuras, principalmente depois da morte dos principais cuidadores ou incapacidade destes para assumir os cuidados do paciente; e com o impacto que a doença tem quer nos principais cuidadores, como noutros familiares, principalmente nos irmãos saudáveis dos pacientes. Apesar das dificuldades expressas pelos participantes, estes também referiram ter recursos disponíveis e facilitadores da adaptação à vivência com a CDG. O apoio de outras famílias CDG foi um dos recursos mais referidos pelos participantes, que valorizam a oportunidade que têm em partilhar experiências e conhecer pessoas em situações semelhantes às suas, diminuindo os seus sentimentos de solidão. Tudo aquilo já referido até então, acaba por contribuir para as estratégias de *coping* utilizadas. Dos relatos dos participantes foi possível identificar a utilização quer de estratégias focadas na emoção, como de estratégias focadas no problema. Apesar do impacto negativo maioritariamente sentido, alguns participantes partilharam experiências e resultados positivos de desenvolvimento pessoal individual e familiar decorrentes da experiência com uma doença rara.

Esta experiência permitiu ainda que muitos participantes, no final da entrevista, partilhassem mensagens que gostariam de passar a novas famílias com pacientes CDG recentemente diagnosticados.

A pertinência do estudo prende-se não só com a sua exclusividade no estudo do impacto da doença rara estudada nos familiares cuidadores, como também com a possibilidade de partilha dos resultados com profissionais de saúde e com familiares em semelhantes situações. O presente estudo chama ainda a importância para a maior atenção que deve ser dada às dificuldades sentidas por este grupo restrito da população, e consequente necessidade de tomada de medidas no sentido de o apoiar e promover a sua melhor adaptação e experiência vivida.

Palavras-chave: Doenças raras; CDG; Sobrecarga dos cuidadores; Coping; Experiências e adaptação familiar; Estudo qualitativo

ABSTRACT

Family caregivers of patients with rare health conditions often experience health, financial, social and emotional consequences due to the burden of care. Congenital disorders of glycosylation (CDG) are a group of rare, metabolic and genetic diseases due to defects in the glycosylation process. Cognitive and physical impairments are inherent to the broad spectrum of symptoms that portray this multysistemic disease, which does not have an effective cure yet. This study aims to explore and to better understand the lived experience and process of adaptation of family members of CDG patients.

Interviews through Skype were conducted with 40 family members (26 mothers, 7 fathers, 5 siblings and 2 grandmothers), from 11 different countries. Participants were related to a child, adolescent or adult patient. Interviews underlined topics related to the lived experience during the diagnosis period, and during the daily life management. A thematic analysis helped to identify the main categories in the data transcribed from the recorded interviews.

Participants reported several emotional reactions when receiving the diagnosis, and factors that eased and/or complicated its acceptance. We identified multiple categories related to the burden experienced by the caregivers of CDG patients, to the psychological impact of this disease and to the concerns and coping strategies most used to deal with the disease's daily challenges and demands. Changes, concerns, demands, resources, and coping strategies varied between participants and their specific situation, however there were much similarities in the reports. Positive experiences and outcomes from living with CDG were also reported, as well as a message for the families of recently diagnosed CDG patients.

This study highlights the burden of care experienced by family members living with CDG patients, calling attention for what can be improved within the health sector to better assist them, and how psico-education can enhance their coping strategies so to reduce the stress often experienced.

Keywords: Rare diseases; CDG; Caregiver's burden; Coping; Family experiences and adaptation; Qualitative study

RESUMÉ

Les membres de la famille aidants les patients ayant des maladies rares expériences souvent des conséquences sanitaires, financières, sociales et émotionnelles dues à la pénibilité des soins. L'anomalie congénitale de la glycosylation (CDG) est un groupe de maladies rares, métaboliques et génétiques dues au défaut du processus de glycosylation. Les déficiences cognitives et physiques sont inhérentes au large spectre des symptômes qui représentent cette maladie multisystémique, qui ne possède toujours pas de remède efficace. Cette étude vise à explorer et comprendre de meilleure manière l'expérience de vie des membres de familles de patients CDG.

Des entretiens ont été menés via Skype avec 40 membres de familles (26 mères, 7 pères, 5 soeurs et 2 grands-mères), de 11 pays différents. Les parents sont liés à patient enfant, adolescent ou adulte. Les entretiens soulignent des sujets liés à l'expérience vécue durant la période de diagnostique, et durant la gestion de la vie quotidienne. Une analyse thématique a permis d'identifier les catégories principales parmi les données retranscriptes des entretiens.

Les participants ont également signalé de nombreuses réactions émotionnelles à la réception du diagnostique, et des facteurs qui ont facilité et/ou compliqué son acceptation. Nous avons identifié de multiples catégories liées aux difficultés vécues par les donneurs de soin des patients CDG, l'impact psychologique de cette maladie et les préoccupations et stratégies d'adaptation les plus utilisées pour faire face aux challenges et demandes de la maladie. Changements, préoccupations, ressources et stratégies d'adaptation varient selon les participants et leurs situations spécifiques, cependant, il y a de nombreuses similarités dans les comptes-rendus. Les expériences positives et les résultats concernant la vie avec CDG sont évoquées, ainsi qu'un message pour les familles avec des patients récemment diagnostiqués de CDG

Cette étude met en lumière la pénibilité du soin expérimenté par les membres de familles qui vivent avec des patients CDG, mettant en avant ce qui peut être amélioré au sein du secteur de la santé pour les assister de meilleure manière, et comment l'éducation psychologique peut améliorer leurs stratégies d'adaptation afin de réduire le stress souvent expérimenté.

Mots-clés: Maladies rares; CDG; Fardeau des donneurs de soins; Expérience et adaptation familiale; Étude qualitative

TABLE OF CONTENTS

INTRODUCTION 1

REVIEW OF LITERATURE 3

1. Congenital disorders of glycosylation 3

1.1. Description 3

1.2. Symptoms 3

1.3. Diagnosis 4

1.4. Treatments and therapies 5

2. Adaptation of families of patients with a chronic health condition 6

3. Adaptation of families of patients with a rare health condition 7

3.1. Feeling different from the others 7

3.1.1. Receiving a diagnosis 8

3.1.2. Access to health care and support 9

3.1.3. Access to information 9

3.2. Consequences for family members caring for a patient with a rare disease……. 10

3.2.1. Family caregivers' concerns 10

3.2.2. Financial burden 11

3.2.3. Social support and social relationships 12

3.2.3.1. Family relationships 12

3.2.3.2. Health and social support 13

3.2.3.3. Support groups 14

3.2.4. Emotional burden and coping strategies 14

METHODS 17

1. Sampling and recruitment 17

2. Participants 17
3. Procedure 19
4. Data collection 19
5. Ethics 20
6. Data analysis 20
RESULTS 22
1. Dimension – *Diagnosis* 22
1.1. Category - *Searching for the diagnosis* 22
1.1.1. Sub-category – *Definition of the diagnosis* 23
1.1.2. Sub-category – *Lived experience* 23
1.2. Category - *Receiving and accepting the diagnosis* 23
1.2.1. Sub-category - *Emotional reactions* 25
1.2.2. Sub-category - *Factors that made the acceptance of the diagnosis harder*…… 26
1.2.3. Sub-category – *Factors that promoted the acceptance of the diagnosis*…… 26
2. Dimension – *Living with CDG in the family* 27
2.1. Category – *Participants' knowledge about the disease* 27
2.1.1. Sub-categories – *General knowledge about CDG*; *Participants' desire to know about CDG*; *Difficulties in explaining CDG to other people*……..... 27
2.2. Category – *Main changes* 28
2.2.1. Sub-category – *Family life* 28
2.2.2. Sub-category – *Instrumental changes* 29
2.3. Category - *Demands and challenges* 29
2.3.1. Sub-category – *For the participant* 32
2.3.2. Sub-category – *For the family* 32

2.3.3. Sub-category – *For the patient* 33

2.4. Category – *Main concerns* 33

2.4.1. Sub-category – *Concerns regarding the present* 35

2.4.2. Sub-category – *Concerns regarding the future* 36

2.4.3. Comparing concerns of participants according to the patients age group..... 36

2.5. Category – *Resources that ease the experience of living with CDG*..... 37

2.5.1. Sub-category – *Social support* 38

2.5.2. Sub-category – *Patient and caregiver as resources* 39

2.5.3. Sub-category – *Health support* 39

2.5.4. Sub-categories – *Educational and therapeutic activities*; and *Financial support*..... 39

2.6. Category - *Coping strategies*..... 40

2.7. Category - *Positive experiences/outcomes* 42

2.7.1. Sub-category – *For the participant* 42

2.7.2. Sub-category – *For the family* 43

3. Dimension – *Messages for other families* 43

4. The perspective of grandmothers and siblings 44

DISCUSSION 46

CONCLUSION 50

REFERENCES 52

APPENDIX[1]

[1] Due to confidentiality policies, transcripts of the interviews will not be shown in this paperwork.

LIST OF TABLES

Table 1. *Participants' characteristics.* 18

Table 2. *Patients' characteristics.* 18

Table 3. *Sub-categories, codes, number of participants (%), and examples for the Category "Searching for the diagnosis".* 22

Table 4. *Sub-categories, codes, number of participants (%), and examples for the Category "Receiving and accepting the diagnosis".* 23

Table 5. *Sub-categories, codes, number of participants (%), and examples for the Category "Participants' knowledge about the disease".* 27

Table 6. *Sub-categories, codes, number of participants (%), and examples for the Category "Main changes".* 28

Table 7. *Sub-categories, codes, number of participants (%), and examples for the Category "Demands and challenges"* 29

Table 8. *Sub-categories, codes, number of participants (%), and examples for the Category "Main concerns".* 33

Table 9. *Sub-categories, codes, number of participants (%), and examples for the Category "Resources that ease the experience of living with CDG".* 37

Table 10. *Sub-categories, codes, number of participants (%), and examples for the Category "Coping strategies".* 40

Table 11. *Sub-categories, codes, number of participants (%), and examples for the Category "Positive experiences/outcomes".* 42

Table 12. *Codes, number of participants (%), and examples for the Dimension "Messages to other families".* 43

INTRODUCTION

Rare diseases are complex, multi-systemic and non-preventable disorders without an effective cure and often life-threatening, which affect a small percentage of the world population (Eurordis, 2009; Griggs et al., 2009). Worldwide, it is estimated that 6 to 8% of the population have a rare disease, although there are probably many individuals undiagnosed (Bellgard et al., 2013). Most of these diseases are genetic disorders, frequently with their onset during the childhood, characterized as disabling and leading to physical and mental impairments (Jaffe, Zurynski, Beville, & Elliott, 2010; Schieppati, Henter, Daina, & Aperia, 2008). A disease is considered rare in Europe when it affects fewer than 1 in 2000 individuals (Eurordis, 2009), in the USA fewer than 1 in 1250 (Schieppati et al., 2008), and in Australia fewer than 1 in 1000 (Zurynski, Frith, Leonard, & Elliott, 2008).

From a public health perspective, it is important to organize systematic public health responses to rare diseases, such as gathering accurate data to support the surveillance and monitoring of these multiple diseases and to guide the care of sick individuals and their families (Bellgard et al., 2013). Although each rare disease affects only a few people in each country, considering the group or rare conditions, these may impact about 50 million patients worldwide, making it necessary to adopt a broad perspective and consider research and treatments for rare diseases globally (Gliklich & Leavy, 2011). It is important to combine efforts to develop and improve diagnostic tools, care and prevention, and to encourage collaborative research (Aymé & Schmidtke, 2007).

Many diagnosed patients and/or their caregivers have little knowledge and understanding of the disease, as do most of the assistant clinicians, since there is a scarcity of research on several of these diseases and reduced dissemination of the existing knowledge among the medical community (Gliklich & Leavy, 2011). To overcome this problem, during the past years several countries have promoted a network of reference centres for rare diseases, aiming to improve patients' access to expert care and the dissemination of updated findings (Schieppati et al., 2008). An example is the importance that has been given to patient registries, recognized as a crucial step to learn more, not only about the disease, but also about the patients themselves (Gliklich & Leavy, 2011).

However, more attention to rare diseases and their impact is still lacking, as these conditions imply a significant burden, not only for the affected individuals, but also for their families, health professionals and the overall community (Jaffe et al., 2010).

REVIEW OF LITERATURE

1. Congenital disorders of glycosylation

1.1. Description

Congenital disorders of glycosylation (CDG) are a group of rare and severe metabolic diseases in which the process of glycosylation is affected, with defects in the synthesis of glycoproteins and glycolipids (Dulary, Potelle, Legrand, & Foulquier, 2017; Jaeken, 2003; Marques-da-Silva et al., 2017). The majority have an autosomal recessive inheritance; among the exceptions is the multiple exostoses syndrome, which has a dominant inheritance (Jaeken, 2003). Until now 104 CDG types were identified, which makes these conditions one of the most rapidly growing group of genetic and metabolic diseases (Jaeken & Péanne, 2017).

In 1980, Jaak Jaeken was responsible for the first observation of some alterations in the process of the glycosylation in monozygotic twin sisters, marking the beginning of the attention given to this process in the human body (Jaeken, 2011). Glycosylation refers to the synthesis of glycoconjugates by attaching glycans to proteins, lipids and other compounds. Nearly all the biological processes count with glycans, with the human body having around 500 genes involved in the processes of glycosylation, thus highlighting the importance of glycans in our functioning (Jaeken, 2003; Monticelli, Ferro, dos Reis Ferreira, Jaeken, & Videira, 2016). Impairments in the process of glycosylation lead to potential defects in biosynthetic pathways affecting the development, growth and functioning of cells (Monticelli et al., 2016), causing developmental alterations, sometimes lethal (Marklová & Albahri, 2007).

CDG occurs worldwide and the most common defect is the phosphomannomutase-2 deficiency (PMM2-CDG). It is characterized by a multisystemic clinical expression that ranges from mild to severe phenotypes (Grünewald, 2009). Its multi-organ nature can be much like other multisystemic disorders, which explains the risks of misdiagnosis and alerts for the importance of an early CDG screening (Jaeken, 2003).

1.2. Symptoms

The impairments in the process of glycosylation affect multiple systems, expressed through a large diversity of symptoms (Marquardt & Denecke, 2003).

Symptoms can vary depending on the subtype of CDG, but in general this rare metabolic disease is characterized by cognitive and physical impairments (de Lonlay et al., 2001; Eklund & Freeze, 2006). Neurological involvement is a major component in most CDG subtypes, mostly due to the cerebellum atrophy, leading to developmental disability, hypotonia, hyporeflexia, ataxia, and in some cases seizures. The immunological system can be affected, with clinical expressions such as allergies, atopy, autoimmunity and recurrent infections (Monticelli et al., 2016). Relevant cardiac complications can be observed, like cardiomyopathy, valvular and septal rhythm disturbances, and pericardial effusion (Marques-da-Silva, Francisco, et al., 2017). Liver involvement is expected since it is a major site of glycosylation, producing most of the glycosylated proteins. Hepatic encephalopathy, ascites, liver fibrosis and cirrhosis, and liver failure are some examples of liver-related implications (Marques-da-Silva, dos Reis Ferreira, et al., 2017). Other symptoms can be found, such as psychomotor retardation, atypical morphology (like facial dysmorphism, microcephaly, inverted nipples and fat pads), failure to thrive, strabismus, nystagmus, stroke-like episodes, scoliosis, retinopathy, peripheral neuropathy, anaemia, cyclic vomiting, diarrhoea and protein-losing enteropathy, and renal failure (de Lonlay et al., 2001; Eklund & Freeze, 2006; Jaeken, 2003; Marklová & Albahri, 2007; Marquardt & Denecke, 2003).

Childhood mortality can happen, although when the child survives and specifically for PMM2-CDG, acute events become less frequent during adolescence, with a stabilization of the mental retardation and peripheral neuropathy during adulthood (i.e., the cerebellar ataxia does not progress any further) (Marklová & Albahri, 2007). However, motor disability may worsen over time and may lead to the loss of independent ambulation and autonomy (Monin et al., 2014). Patients who reach adulthood rarely are totally independent, and the most common phenotypes include intellectual disability, speech disorder, visual loss, neuropathy and ataxia (Wolthuis, Janssen, Cassiman, Lefeber, & Morava-Kozicz, 2014).

1.3. Diagnosis

As with most rare diseases, diagnostic is often a difficult and prolonged process. Some CDG patients present neither neurological impairments, nor mild learning disorders, thus making the diagnosis even more difficult to reach (Wolthuis et al., 2014).

Screening for CDG can also be difficult when the defect is allocated in a restricted organ or system (Jaeken, 2003).

Serum transferrin isoelectrofocusing is by far the most used screening method for glycosylation defects linked to a deficiency in sialic acid, due to its low cost, low sample requirement and availability in most clinical laboratories. However, it has the disadvantage of not allowing to detect the specific defected gene and of being inconclusive or ineffective for some CDG subtypes. Prior and complementary to the serum transferrin isoelectrofocusing analysis, there are other diagnostic tests that can facilitate the final diagnosis of CDG, such as ophthalmic and electromyographic examination, X-ray, ultrasound, magnetic resonance imaging, and computer tomography (Marklová & Albahri, 2007). Nowadays the analysis of transferrin by isoelectric focusing (TIEF), by high performance liquid chromatography (HPLC), or by capillary electrophoresis (CE), are considered the front-line screening methods to diagnose CDG (Van Scherpenzeel, Willems, & Lefeber, 2016). Despite these, more precise analysis are required to confirm the defected gene (Marklová & Albahri, 2007). Molecular techniques, including next generation sequencing with a CDG gene panel, containing all the genes known to cause CDG, and whole exome sequencing (WES) are among the most accurate diagnostics for CDG (Jaeken, Lefeber, & Matthijs, 2015). Since no general clinical guidelines for CDG screening exist, it is recommended to screen any child with unclear multisystem dysfunction and multiple symptoms, such as the ones described above (Marklová & Albahri, 2007). Because of the risks of misdiagnosed or undiagnosed patients, it is important to include CDG as an option for a differential diagnosis in adults who present unexplained neurological features and non-progressive intellectual disability, facial dysmorphism, abnormal fat distribution and some congenital malformations (Wolthuis et al., 2014).

1.4. Treatments and therapies

Treatment is symptomatic as there is no cure for this group of diseases. Concerning the most common type of CDG, the PMM2-CDG, there are several strategies to manage some of its symptoms. Maximizing the intake of calories through food supplements help to correct the failure to thrive. Sometimes, the placement of a nasogastric or a gastrostomy tube is necessary, to facilitate nutritional support. Speech therapy and oral motor therapy aim to facilitate the transition to oral nourishment and to

improve speech that is usually impaired due to developmental delay. This delay can also be improved by occupational and physical therapy. Strabismus is commonly present in PMM2-CDG patients, and so it is important to have an early ophthalmological intervention to preserve vision. For situations of stroke-like episodes, there is supportive therapy for the recovery period, including hydration and physical therapy. The low levels of coagulation factors, when coagulopathy is present, can be corrected through the infusion of fresh frozen plasma. Orthopedic impairments such as scoliosis can be corrected by surgeries, or managed through physical therapy. There are also some rehabilitation aids including wheelchairs, walkers and other transfer devices that may facilitate mobility (Sparks & Krasnewich, 2005).

Most of the treatments are just partially effective, reflecting one of the most serious problems of CDG. The only known effective treatments are oral administration of supplements for the MPI-CDG and SLC35C1-CDG types, with patients showing notorious improvements (de Lonlay & Seta, 2009; Schachter & Freeze, 2009). Oral supplementation was recently shown to be also effective for the TMEM165-CDG and PGM1-CDG subtypes, with patients improving in biochemical and clinical parameters (Morelle et al., 2017; Wong et al., 2017). Other interventions aim to correct specific anomalies, improving the function of specific organs or systems and controlling specific symptoms, such as seizures and infections, for example. These treatments include oral administration of supplements, heart or liver surgeries, or stem cell transplantation (Jaeken & Péanne, 2017).

2. Adaptation of families of patients with a chronic health condition

Most literature on the adaptation of families with chronically ill patients focus the adaptation of parents, and less frequently siblings, of children and adolescents with chronic conditions. As most CDG families start their adaptation when the patient is an infant or young child, we will focus mostly on this research.

Families with children with a chronic condition face the same stresses and strains of families with healthy children. However, there are additional stresses brought about by the illness (Cohen, 1999). The family unit and each family member individually are challenged with demands such as understanding of the health condition, the management of the daily care, the need to adapt family routines and to establish continued and intense relationships with health and educational professionals (Knafl, 1998).

Parents' roles change as they become the patients' main health caretaker. Parents must acknowledge that life will be forever different and that there is a new reality to accept and to deal with (Kepreotes, Keatinge, & Stone, 2010). A poor adjustment to the main demands of the disease increases the risk of parental emotional distress (Cohen, 1999; Wallander & Varni, 1998), who experience greater stress than parents of healthy children (Cousino & Hazen, 2013).

3. Adaptation of families of patients with a rare health condition

A rare disease is primarily a chronic disease, sharing most of the demands within the adaptation process to a pediatric chronic condition. However, there are unique burdens related to the rarity of these health conditions. The challenges are multidimensional and represent a daily burden (Pelentsov, Fielder, Laws, & Esterman, 2016), with the demands for resources and skills going beyond the normally required by parenting a child (Case-Smith, 2004). Despite the specificities of each rare condition, which affect the child and family members in unique ways, the needs of these families are largely universal (Pelentsov, Laws, & Esterman, 2015).

There is limited understanding of how rare diseases affect families' lives and how these families adapt to these impacts. Political, scientific and medical communities have given little attention to individuals affected with a rare health condition and to their families (Anderson, Elliott, & Zurynski, 2013; Dodge et al., 2011), but some research has pointed to the main areas of hardship and distress.

3.1. Feeling different from the others

Parents of children with rare conditions often feel isolated, as if they were the only ones in such situation, which can lead them to experience instrumental, health, and social stress (Grut, Kvam, & Lippestad, 2008). These feelings are often caused by the difficulty and delay in receiving a final diagnosis, the lack of information and little specific knowledge about the disease from the assisting health team, the limited access to health support and services, and the lack of effective treatments (Anderson et al., 2013; Feltmate, Janiszewski, Gingerich, & Cloutier, 2015; Knight & Senior, 2006; Moreno García, Antequera Jurado, Aires González, Colado Huertas, & Díaz Rubiales, 2008).

3.1.1. Receiving a diagnosis

Diagnosing a rare disease is one of the greatest challenges for the medical and scientific community. Usually this is a lengthy process, experienced with much suffering by the families who often must wait long periods before receiving the correct diagnosis, with some of them never getting one (Dodge et al., 2011). Lack of effective screening tests and lack of health professionals training to recognize signs and symptoms (Zurynski et al., 2017), may lead families to search for multiple professionals and to undergo unnecessary tests before receiving a final diagnosis (Anderson et al., 2013; Weng et al., 2012). A lengthy diagnosis delays the access to treatments and in some cases even leads to maintaining inappropriate treatments (Anderson et al., 2013; Weng et al., 2012; Zurynski et al., 2017).

Receiving a diagnosis of a rare disease is usually a traumatic and unanticipated experience. Thus, this communication must be conducted with sensitivity and in a supportive environment (Zurynski et al., 2017), with parents highlighting the importance of a professional but warm attitude from the health professional (Havermans, Tack, Vertommen, Proesmans, & de Boeck, 2015). A qualitative study about parents' experiences of receiving a diagnosis of a severe disease showed that their main needs are a cooperative attitude from the health team, provision of specialized information, with consideration of all the possible evolution paths, an empathic and personal approach, and talking about the child as a person and not a case study (Graungaard & Skov, 2007).

Parents usually recall vividly the moment they received their child's diagnosis and are able to describe all the small details about the situation (Havermans et al., 2015). On one side, it is a strong emotional process for parents, who report feelings of anger, shock, anxiety, denial, sadness or loss. On the other side, some consider receiving the correct diagnosis as a relief, since it allowed to put an end to the doubts and the guilty feelings about their child's disease (Pelentsov, Laws, et al., 2015). As such, achieving an early and correct diagnosis is highly valued by parents. Being able to reach some degree of certainty about the disease enables parents to explain it to other persons and to plan the care of the child, decreasing their stress and anxiety related to the child's condition and his/her future (Pelentsov, Laws, et al., 2015; Zurynski et al., 2017, 2008).

Independently of the time taken until the final diagnosis, parents refer that psychological support should be offered at this stage (Zurynski et al., 2017). Beside this

lack of psychological support, health providers' lack of scientific knowledge about many rare diseases, or inadequate and insufficient information about the disease, contribute to the dissatisfaction of parents with the way this important phase was handled (Anderson et al., 2013; Zurynski et al., 2017).

3.1.2. Access to health care and support

Most generalist health professionals have little experience and insufficient knowledge about specific rare diseases and this can cause frustration and dissatisfaction in parents who expect these professionals to give them accurate information, reassurance and guidance (Pelentsov, Laws, et al., 2015). The lack of providers' awareness, knowledge and experience in the field of rare diseases perceived by parents, and the many obstacles to contact an expert in the specific health condition, can lead parents to feel their child is lacking the necessary care (Pelentsov, Fielder, & Esterman, 2015). These families sometimes must travel long distances to see an expert and get specialized support and answers to their doubts (Anderson et al., 2013; Dodge et al., 2011; Pelentsov, Laws, et al., 2015).

Despite all difficulties and obstacles, most families manage to find a health team that is able to provide the multidisciplinary care that the patient need. However, they often complain about not feeling well integrated in the health team (Aubeeluck, Buchanan, & Stupple, 2012; Boyer, Drame, Morrone, & Novella, 2006; Graungaard & Skov, 2007). Comparing themselves with parents of children with more common chronic conditions, such as asthma or diabetes, parents perceive an inequity in health care and may feel insecure about how adequately the patient needs are being met (Pelentsov et al., 2016; Schieppati et al., 2008).

The need to deal with multiple providers is also a burden for some families. Anderson and collaborators (2013) conducted a qualitative study with Australian families living with a rare metabolic disease, where families suggested that a better coordination of care, and the use of electronic health records that could be accessed by all the health professionals within the health care team, could improve their experience of care.

3.1.3. Access to information

Independently of the reduced specialized knowledge of health professionals about rare conditions, parents usually have trouble in accessing information about their child's

disease, namely information concerning the evolution and prognosis (Moreno García et al., 2008). Most parents actively search for information, especially using the resources available online. They feel the need to look for accurate and understandable information about their child's disease (Havermans et al., 2015; Zurynski et al., 2008), and about the multiple problems of caring for the patient, thus adding one more task to all their multiple tasks as a caregiver (Aubeeluck et al., 2012). However, the information available about most rare diseases is scarce, often too broad and technical, difficult to understand and to relate to the specific situation each family is living (Aubeeluck et al., 2012; Kim et al., 2010). Beside this, accessing the correct information in the world wide web is another challenge (Pelentsov, Laws, et al., 2015), and the multiple, oftentimes divergent information, may have a negative impact on parents (Havermans et al., 2015).

3.2. Consequences for family members caring for a patient with a rare disease

The daily life of families with patients with a rare health condition is usually marked by the disease management and consequences (Grut et al., 2008). Family caregivers must make multiple changes in their current routines and projects, and they have their lives limited by the need to care for the patient, frequently feeling that their personal life is solely occupied with their caregiver's role. All family members may be emotionally affected , but the main caretaker is specially impaired in her/his professional and social life (Aubeeluck et al., 2012; Gallop, Wild, Nixon, Verdian, & Cramer, 2009; Jensen et al., 2017; Malcolm, Gibson, Adams, Anderson, & Forbat, 2013; Pelentsov et al., 2016; Roper, Allred, Mandleco, Freeborn, & Dyches, 2014; Zurynski et al., 2008).

3.2.1. Family caregivers' concerns

Parents of children with chronic health conditions usually report concerns regarding the present daily life and concerns regarding the future (Coffey, 2006; Gallo, Hadley, Angst, Knafl, & Smith, 2008; Moreno García et al., 2008).

Regarding the current situation, parent's concerns are focused on the patient, but also on themselves and the other family members. Health insurance and financial strains related with the patient's health care are an important worry, as is their ability to conciliate their work responsibilities with the care of the patient (Gallo et al., 2008), while maintaining a balanced family life (Coffey, 2006). The impact on siblings is another

important concern for parents who fear long-term psychological and emotional consequences (Pelentsov, Fielder, et al., 2015; Pelentsov, Laws, et al., 2015).

Many parents also struggle to support and help their ill child to overcome their personal difficulties and to accept the disease's limitations and its consequences (Moreno García et al., 2008). The patients' psychosocial and physical well-being and their social integration at school or work are some examples of parents' concerns regarding their ill children (Moreno García et al., 2008).

Concerns regarding the future are mostly related with the future professional opportunities for the child, considering his/her physical and cognitive limitations, and the worry of anticipating a time when they will no longer be able to take care of the patient. These concerns are common in most parents who have a child with a chronic health condition and even more so when this is a rare disease, since there is more uncertainty about the evolution of the patient and his future degree of autonomy (Moreno García et al., 2008).

3.2.2. Financial burden

Parents of children with chronic conditions usually report some financial burden inherent to their child's condition that may imply the need to make important life options. Expensive treatments, specialized equipment, frequent medical appointments, structural adaptations in the house or the need to move to a new one, special educational services, and lack of insurance, are among the most cited motives of heavy financial burden for these families (Coad et al., 2015; Michalík, 2014; Pelentsov, Fielder, et al., 2015; Pelentsov et al., 2016; Read, 2003; Zurynski et al., 2008).

To meet the needs of caring for the patient, it is common that one of the parents reduces the working hours or even stops working, which also contributes for greater financial hardship (Pelentsov et al., 2016), thus increasing family stress (Coffey, 2006). An international cross-sectional study with caregivers of patients with Duchenne muscular dystrophy estimated that between 27% and 49% of caregivers had to reduce their working hours or stop working to take care of the child (Landfeldt, Lindgren, & Bell, 2014).

In almost all the families in this situation, mothers are the ones more affected, since they are the ones who assume most of the responsibilities of care (Grut et al., 2008;

Pelentsov, Laws, et al., 2015; Weng et al., 2012). These mothers may become more socially isolated (Coffey, 2006). When there is only one parent in the family, the financial burden falls back on him/her, creating higher difficulties to manage simultaneously working and caring for the patient (Pelentsov, Laws, et al., 2015).

3.2.3. Social support and social relationships

The increased needs for social support of these family caretakers are mostly due to social isolation, loneliness and feeling disconnected, with almost all social relationships being affected by the caring responsibilities that make it difficult to attend social activities (Jensen et al., 2017; Pelentsov, Laws, et al., 2015). Some parents report a narrowing of their social network due to the unavailability to attend social events or because other people have trouble understanding their experience (Pelentsov et al., 2016). Lack or reduced social support increases the difficulties in coping with the challenges of caring for a chronically ill child, with parents feeling overburdened and emotionally exhausted (Pelentsov, Laws, et al., 2015). This burden may be alleviated when family caregivers benefit from the support from family and friends, health and social services, and from families in similar conditions as theirs (Dogba, Rauch, Douglas, & Bedos, 2014; Read, 2003).

3.2.3.1. Family relationships

Having a family member with a rare health condition affects the quality of life of all family members and adds strain to the family as a whole (Moreno García et al., 2008). Extended family members are sometimes perceived as uneasy and fearful about taking care of the patient, probably on account of their limited knowledge and experience with dealing with the clinical manifestations of the disease (Bruns & Foerster, 2011), but also because family caregivers may feel overprotective of the patient. However, some parents also report positive family experiences. The patients themselves are perceived as a source of motivation and strength for the other family members. Stronger relationships within the family and a larger social network, a greater knowledge and sensibility about disabilities, not taking life for granted, and a higher level of tolerance and patience, are some positive experiences reported by these parents (Paster, Brandwein, & Walsh, 2009).

Beside the individual physical and psychological impact, parents may experience a negative impact in their couple relationship, frequently reporting marital dissatisfaction

(Berge, Patterson, & Rueter, 2006; Dellve, Samuelsson, Tallborn, Fasth, & Hallberg, 2006; Gallop et al., 2009; Pelentsov, Fielder, et al., 2015). The couple relationship may be affected by the daily burdens of caring for the patient and by the lack of opportunities to spend quality time with each other (Dellve et al., 2006; Pelentsov, Laws, et al., 2015). However, some parents find in each other their main source of support. The life partner is commonly referred as the most supportive person, who shares the care for the child, the management of the family and who provides the much needed emotional support (Bruns & Foerster, 2011).

Studies about the experiences of siblings of children with cancer or other chronic health conditions have shown both positive and negative outcomes (Kao, Romero-Bosch, Plante, & Lobato, 2012; Mazaheri et al., 2013; Nolbris, Enskär, & Hellström, 2007; O'Brien, Duffy, & Nicholl, 2009; Read, Kinali, Muntoni, Weaver, & Garralda, 2011; Sharpe & Rossiter, 2002; Woodgate, 2006). The ability to empathise with others, acquiring an enhanced maturity and resilience and strengthening bonds with all family members are some of the positive outcomes reported (Manor-Binyamini & Abu-Ajaj, 2012; Moreno García et al., 2008; Roper et al., 2014). On the other hand, some siblings show sleep problems, lower cognitive development scores, behavioural problems, pessimism concerning the future and psychological disturbances, with intense feelings of sadness and anger, avoidance and increased arousal (Mazaheri et al., 2013; O'Brien et al., 2009; Sharpe & Rossiter, 2002). Siblings of children with rare life-limiting conditions look forward to protect the patient (Santos, Pires, Soares, & Barros, 2017), their other healthy siblings, their parents, but also themselves (Malcolm et al., 2013).

3.2.3.2. Health and social support

Parents of children with a rare health condition commonly report being dissatisfied with the support received from health professionals, their level of awareness and knowledge about the child's disease, and complain about not feeling recognized as part of the health care team (Aubeeluck et al., 2012; Boyer et al., 2006; Graungaard & Skov, 2007).

Additionally, some parents feel it is solely up to them to manage and take responsibility about their child's healthcare, instead of having a health provider assuming the main direction in the management of the health condition. They feel forced to get more involved that they would like in all aspects of the health care, assuming the role of

"expert" and making important decisions (Grut et al., 2008; Pelentsov, Fielder, et al., 2015). They assume tasks related to developing an expert knowledge about the disease, searching for updated information, and advocating for new treatments, therapies and interventions (Pelentsov et al., 2016). Even when they find a main health provider who is an expert in the disease, parents experience difficulties when they have to contact other health care professionals that are not familiarized with the disease (Siddiq et al., 2016).

Oppositely, a good relationship between parents and the healthcare team has been associated to a better ability to cope and adapt to the disease (Graungaard & Skov, 2007). When adequately supported by healthcare providers, family caregivers can benefit from more effective resources (Coad et al., 2015).

3.2.3.3. Support groups

To meet families in the same situation and with the same diagnosis seems important for parents of children with a rare disease, who experience great limitations in their daily lives and a sense of isolation (Grut et al., 2008). Communicating and sharing experiences with families in similar circumstances is referred by parents as something that helps them to better cope, since they feel understood (Bogart et al., 2017; Glenn, 2015; Pelentsov, Laws, et al., 2015). Receiving mutual support and encouragement, sharing a social identity and having a sense of belonging, help parents to cope with their life situation, decreasing their stress and empowering them to manage the multiple tasks of the daily care of the patient (Coad et al., 2015; Mathiesen, Frost, Dent, & Feldkamp, 2012; Shilling et al., 2013). Support groups promote the connection between parents and patients with similar conditions and often organize the access to and collaboration with the most advanced medical research groups (Grut et al., 2008; Hennekam, 2011). In many countries, families of patients with rare diseases have organized advocacy and patient groups, as an effort to overcome the lack of information and support and promote research about rare diseases (Schieppati et al., 2008).

3.2.4. Emotional burden and coping strategies

As above described, diagnosis delays, lack of information and difficulty in accessing appropriate health care services and support are typical challenges faced by families of patients with a rare health condition. These challenges bring about important stress associated with social isolation, family conflict, financial and professional burden,

uncertainty about the future, perception of lack of control and competency. Family caretakers experience important emotional burden, with recurrent feelings of sadness, depression and anxiety (Dellve et al., 2006; Dogba et al., 2014; Gallop et al., 2009; Kim et al., 2010; Lipinski, Lipinski, Biesecker, & Biesecker, 2006; Senger, Ward, Barbosa-Leiker, & Bindler, 2016; Weng et al., 2012; Williams et al., 2009; Zurynski et al., 2008).

Coping strategies can help caregivers to face these challenges and reduce the daily stresses due to their child's disease (Paster et al., 2009). However, they can lack the ability to cope effectively or use less effective strategies (Kim et al., 2010; Pelentsov, Fielder, et al., 2015; Pelentsov, Laws, et al., 2015).

Lazarus and Folkam (1984) define *coping* as *"constantly changing cognitive and behavioural efforts to manage specific external and/or internal demands that are appraised as taxing or exceeding the resources of the person"* (pp. 141). These authors developed a model that distinguishes two types of coping: emotion-focused and problem-focused coping. Emotion-focused coping refers to efforts to reduce or regulate emotional reaction to stress. Coping strategies intent the modification of the emotions related to the stressful event, and not of the event itself. This type of coping includes strategies used by the individual to avoid the stressful event (avoidance, distraction), and strategies where the individual does a re-interpretation of the event (positive re-evaluation, minimization, attribution of a meaning). Problem-focused coping strategies aim to modify the stressful situations, something not achievable through the previous type of emotion-focused coping. This type of coping involves active efforts to modify or better manage the stressful event. It includes cognitive and motivational strategies, such as searching for information and learning new skills and procedures or planning the resolution of the problem by using effective strategies (Lazarus & Folkam, 1984)

The severity of the stress perceived by caregivers of patients with a rare health condition depends on the primary appraisal (to perceive a threat to one's self) and secondary appraisal (to identify a potential response to the threat) (Lazarus & Folkam, 1984). In the case of the caregivers of a patient with a rare disease, the lack of knowledge or understanding about the disease, the doubts and uncertainties about the future, the challenges associated with the management of the illness, and the perception of lack of social and professional support might hinder the process of coping, since both primary and secondary appraisals may be affected (Picci et al., 2015).

Caregivers of patients with rare health conditions may differ in their ways of coping, depending on individual factors, the situation within the family and the specific features of the disease (Dellve et al., 2006). Easily discriminating potential stressors, which resources are available, and feeling motivated to deal with their difficulties allow parents to better manage their stress, coping more adaptively with their life challenges (Kumari, 2017).

Parents of children with rare health conditions tend to rely on religion as a coping mechanism. This may be because of their greater difficulty in understanding the disease, due to its rarity, when compared to parents of chronically ill children (Picci et al., 2015). When caring for a child with a life-limited condition, parents tend to show a sustained optimistic and hopeful perspective and to use minimization, by referring to their child's disease as less severe than the one of other children with similar health conditions (Coad et al., 2015). Other strategies such as normalization and positive re-evaluation have also been reported, probably to allow to continue profiting from life while managing daily stresses and demands (Atkin & Ahmad, 2000). When well accomplished, normalization is perceived as positive strategy and a source of motivation by parents who use it (Knafl, Darney, Gallo, & Angst, 2010).

Active coping strategies and future-oriented thinking was found to be used by family caregivers of children with inherited metabolic diseases (Siddiq et al., 2016). For instance, anticipating future stressors to prevent or reduce their impact helped caregivers to better adjust to the daily management of the disease (Siddiq et al., 2016). Other active coping problem-focused strategies reported by parents of disabled patients with chronic and rare health conditions include searching for social support (McGill Smith, 2014; Senger et al., 2016), like medical services (Katz, 2002); organizing activities believed to promote the development of the patient (McGill Smith, 2014); promoting the general quality of life of the family (Katz, 2002); and searching for information about the disease (Gundersen, 2011).

This study aimed to explore the experience of living with a patient with CDG and the process of adaptation of CDG patients' caregivers and family members. To increase the knowledge about the experience of family caregivers of patients with CDG, this work aimed to understand: (1) the daily demands and challenges of the disease, (2) the main concerns and subjective needs of family caregivers, (3) the resources that facilitate the adaptation to the disease, and (4) the coping strategies reported as most effective.

METHODS

This study was conducted in close collaboration with the Portuguese Association of Congenital Disorders of Glycosylation and other Rare Metabolic Diseases (APCDG-DMR), whose endorsement and support made it possible. The letter of this collaboration can be found in Appendix A.

1. Sampling and recruitment

Participants were included if they were a close family member of a patient diagnosed with CDG. By close family member, we refer to the persons with a close and frequent contact with the patient and who have total or partial responsibility over the care and treatment of the patient. The patient could be a child, an adolescent or an adult and all types of the disease were considered, as long as there was a primary diagnosis of CDG.

Introductory emails containing study information were sent by APCDG-DMR to potential participants, with detailed information about the study aims and conditions attached (Appendix B). After the potential participants manifested initial availability, they were directly contacted by email by the main researcher, to arrange a suitable date and time for a skype interview. A consent form (Appendix C) was attached to the emails. A maximum of three attempts were made to contact family members that had first agreed to participate. If no response was forthcoming or the family declined participation, no further contact was made.

Forty-five invitations were sent out, and 40 interviews were made.

2. Participants

The 40 participants included 26 mothers, 7 fathers, 5 adolescent and adult siblings and 2 grandmothers. Since CDG is a rare disease, our sample was dispersed geographically by several countries and had various nationalities. These 40 participants were related to a total of 30 CDG patients. The patients presented five sub-types of CDG. All the family members participated individually in the interviews, except for five couples (mother and father) who participated conjointly. A summary of the socio-demographic and clinical data can be found in Tables 1 and 2.

Table 1. *Participants' characteristics.*

Participants	**N**	**%**
Kinship with the patient		
Mother	26	65
Father	7	17.5
Sibling	5	12.5
Grandparent	2	5
Total	**40**	**100**
Participants per age of group of the patient		
Child	21	52.5
Adolescent	7	17.5
Adult	12	30
Total	**40**	**100**

Table 2. *Patients' characteristics.*

CDG patients	**N**	**%**
Group of age		
Child	15	50
Adolescent	5	16.67
Adult	10	33.33
Total	**30**	**100**
Type of CDG		
ALG11-CDG	1	3.33
DPAGT1-CDG	2	6.67
DPM1-CDG	1	3.33
PIGN-CDG	1	3.33
PMM2-CDG	25	83.33
Total	**30**	**100**
Type of diagnosis		
Early diagnosis (first 2 years of age)	16	53.33
Between 2 – 5 years old	10	33.33
Late diagnosis (after 5 years old)	4	13.33
Total	**30**	**100**

Country of residence		
Australia	2	6.67
Canada	1	3.33
France	3	10
Ireland	1	3.33
Israel	2	6.67
Portugal	3	10
Spain	4	13.33
Sweden	2	6.67
Switzerland	1	3.33
United Arab Emirates	1	3.33
United States of America	10	33.33
Total	**30**	**100**

3. Procedure

Due to the geographically dispersed sample, interviews were conducted through a phone call using the software Skype™ - Version 7.36.0.101 (Skype Communications SARL). All the interviews were audio-recorded using the software Callnote Video Call Recorder for Skype (Kanda Software). Most of the interviews were conducted in the native language of the participants. When the researchers were not fluent in the native language of a participant, he/she was asked to choose another language in which he/she felt comfortable. Most interviews were conducted by the main researcher, who was present in all of them; two other team members helped to conduct the interviews in French and in Spanish. Interviews ranged from 25 minutes to one hour and a half, with a mean time of 50 minutes.

4. Data collection

A semi structured interview script was developed to aid the interview dynamic (Appendix D). After thanking the participant and highlighting the important of each individual contribution, a series of open-ended questions were formulated. Topics covered by the script were related with the family caregivers' experiences regarding the daily disease management and its demands, the impact of the disease on the family

relationships, their satisfaction with health and social services, their most important needs and concerns, and the level and sources of social support. Participants were encouraged to direct the conversation to areas that they considered significant to them regarding their experiences and needs. The questions were adapted to the interviewed participant as this was a parent, a sibling or a grandmother. The interviews ended when all the relevant topics were covered and participants reported not having anything else to add.

5. Ethics

Ethical approval was obtained from the Ethics Committee of the Faculty of Psychology of the University of Lisbon. Verbal and written explanations were given to participants before they were requested to give written consent for the interview. The informed consent included: (1) a description of the project purpose and procedures; (2) an explanation that tapes would be securely stored and destroyed at the end of the study; (3) information that the participants could interrupt the interview at any stage; and (4) reassurance that confidentiality would be preserved throughout all stages of the research and dissemination. All participants provided written informed consent prior to the interview, and specifically authorized the audio recording of the interview. As families were from different nationalities, the informed consent was translated in English, Portuguese, French and Spanish.

6. Data analysis

Interviews were audio-recorded and transcribed verbatim. When performed in other language, the interviews were translated to English, so that all data was in the same language. Data were analysed with Nvivo 11 Pro for Windows, which facilitated exploratory and qualitative analysis.

Like most exploratory studies, the current study used the thematic analysis to identify, analyse and describe dimensions, categories and sub-categories identified in the data. Braun and Clarke (2006) define this analysis as a flexible process with sequential phases. The first phase included the familiarization with the data. Written transcripts were read several times and compared to original recordings to ensure accuracy. Through reading and re-reading the transcripts, it was possible to gain deeper understanding of the information, and identify emerging topics and dimensions. An initial codification was made in the second phase, allowing the organization of the data in more specific codes.

The Nvivo 11 Pro for Windows allowed this collection and organization of data in codes, and later its analysis. After, in the third phase, these codes were assembled, creating a primary system of subcategories and categories. Dimensions, categories, sub-categories and codes related with all the data were revised in the fourth phase. In the fifth phase, an overall rectification the coded data and of the nominations given to the dimensions, categories, sub-categories and codes was made. We arrived to a final system of categories which resulted from a continuous process of codification, interpretation and re-codification of the data. This final system provided a quantification of coded data. Finally, the sixth phase consisted in the crossing of the results of the data analysis with the aim of the study and theoretical framework.

RESULTS

In this chapter, we present the results of this study. The content analysis allowed to identify three main dimensions – *Diagnosis*, *Living with CDG in the family* and *Messages for other families*. In each main dimension, we included different categories and sub-categories that were built from the codes that emerged from the topics covered in the interviews, following the objectives of this investigation.

1. Dimension – *Diagnosis*

This dimension includes the categories *Searching for the diagnosis* and *Receiving and accepting the diagnosis*, that are presented below.

1.1. Category - *Searching for the diagnosis*

Table 3. Sub-categories, codes, number of participants (%), and examples for the Category "Searching for the diagnosis".

Sub-categories	Codes	Number of participants (%)	Examples of answers
Definition of the diagnosis	Hypothesis of probable diseases	8 (20%)	*"They had a list of possible diagnosis and they tested her for a lot of things she could have."*
	Uncertainty about the disease	6 (15%)	*"We saw a lot of doctors, we went to other cities to see doctors, and nobody knew what it was."*
	Wrong diagnosis	6 (15%)	*"We had two wrong diagnosis – muscular dystrophy and one other."*
Lived experience	Difficulties with health care services	18 (45%)	*"We saw a lot of doctors, we went to a lot of different hospitals, we went to other cities."*
	Intense negative emotions	15 (37,5%)	*"I felt everything was out of my control. It was overwhelming."*
	Family life management	2 (5%)	*"I was staying with my grandparents or friends because my parents were always going to appointments and exams." (a sibling)*

1.1.1. Sub-category – *Definition of the diagnosis*

Until reaching a final diagnosis, family caregivers reported that physicians raised different *hypothesis of probable diseases*, or were just *uncertain regarding their child's disease*; a minority first received a *wrong diagnosis* that lasted until the correct diagnosis of CDG was finally made.

1.1.2. Sub-category – *Lived experience*

Participants experienced several *difficulties with healthcare services* during this search for the diagnosis, which was described as frustrating. Some families had to see multiple health professionals from different specialties, they had to attend several medical appointments, sometimes in different health centers and even in other cities or countries, and the child had to go through several tests. Caregivers complained about the lack of knowledge and experience of health professionals regarding CDG as a factor that contributed to the difficulties in achieving a correct diagnosis.

The difficulties inherent to this process triggered *intense negative emotions*. Some parents reported feeling sad and in shock when realizing their child could have a disability, and experiencing guilt because they felt some level of responsibility for the disease. Feelings of frustration and anxiety were related to a perception of lack of control and uncertainty regarding the future.

During this time, difficulties in *family life management* were associated with the time consumed with all the medical exams and tests that reduced the ability to pay attention to the other children. Siblings recalled being difficult to do not have their parents at home most of the time.

1.2. Category - *Receiving and accepting the diagnosis*

Table 4. *Sub-categories, codes, number of participants (%), and examples for the Category "Receiving and accepting the diagnosis".*

Sub-categories	Codes	Number of participants (%)	Examples of answers
Emotional reactions	Relief	12 (30%)	*"For me, CDG was much better and not so serious as the other diseases, it was a big relief for all of us."*

	Anxiety	12 (30%)	*"The uncertainty was creating a huge anxiety in both of us."*
	Despair	9 (22,50%)	*"My biggest question was how long he was going to live."*
	Intense feelings of sadness	5 (12,5%)	*"I was very sad, there was no positive things at that moment."*
	Shock	3 (7,5%)	*"I could not hear or understand anything at that moment."*
	Mourning for the expected lost healthy child	3 (7,5%)	*"I felt like grieving for the baby I had imagined in my head and in my heart, my child would never be like I had imagined."*
	Happiness	3 (7,5%)	*"I was so happy, I could not believe that after so many time I could know which disease it was."*
	Neutral	3 (7,5%)	*"Having a diagnosis did not had an impact on me, because I had taken care of her for so long that the only difference was having a name for her disease."*
	Anger	1 (2,50%)	*"At the moment, I felt anger."*
Factors that made the acceptance of the diagnosis harder	Perceiving the disease as very severe	13 (32,50%)	*"It was really hard because the doctor gave us the worst-case scenario and we felt we had to take care of him every day like he would die the next day."*
	Barriers in accessing information	8 (20%)	*"They only gave us a piece of paper and said that was everything known about the disease."*
	Difficulties in connecting with other CDG families	4 (10%)	*"It's a disease that is being researched, yet there must be some kids that are not diagnosed yet and it took us a while until we get connected to families with the same diagnosis."*
	Difficulties in getting support and guidance from health professionals	4 (10%)	*"When the doctor told us it was CDG he did it in a very cold way, he didn't explain anything and we left without knowing what was the next step. He didn't say where we could get help, which kind of help, nothing."*

Factors that promoted the acceptance of the diagnosis	Support from other CDG families and CDG associations	7 (17,5%)	*"Finding the online FB group with other CDG families was what helped me the most because I could ask them questions and they knew a lot."*
	Support from health professionals	6 (15%)	*"To go to this clinic helped us because we had more information there and we felt more secure about the care he could receive there."*
	Support from life partner	5 (12,5%)	*"The most helpful at that moment was my husband."*
	Perceiving the disease as less severe	4 (10%)	*"We searched and we saw there were things that we could do for CDG, he was not going to die, he could have quite a happy life."*
	Support from family members, friends and work peers	4 (10%)	*"The biggest support were our parents, they were very supportive and stood by our side."*

1.2.1. Sub-category - *Emotional reactions*

Receiving the diagnosis of CDG triggered different emotional reactions. Although most of the family members recalled the moment of being told the diagnosis with some detail, parents were those who reported more diverse emotional reactions. Some siblings were not present in this moment and only found out about the diagnosis through the parents, and some were too young to understand it. Grandmothers were also not present, but recalled the moment they knew about the diagnosis through the parents of the patient.

Participants reported *anxiety* due to the uncertainty regarding the evolution of the disease, the future of the child and of the whole family. In some cases, *despair* was an immediate answer to the communication of the diagnosis, due to the fear of premature death. *Intense feelings of sadness* were also reported, with family members feeling truly sad for the patient, considering the present situation and the future. Participants also reported *shock* when receiving the diagnosis, describing their inability to hear or understand what health providers were explaining. Other negative emotions were less often reported, such as *mourning for the expected lost healthy child* and *anger*.

However, receiving the diagnosis also brought some *relief*, as parents could stop feeling guilty, they could reach some degree of certainty about what to expect and have an opportunity to plan the future, and identified the disease as less severe than the other hypothesized diagnosis. A few parents felt *happy* for finally knowing the diagnosis. Finally, some participants who received a diagnosis after many years of adaptation the situation, described *neutral impact.*

1.2.2. Sub-category - *Factors that made the acceptance of the diagnosis harder*

Due to various reasons reported by participants, the acceptance of the diagnosis was harder than expected. For most of them, CDG was *perceived as a very severe disease*, thus making it difficult to accept it. This perception was based on the information provided by the health professionals or searched online. Participants reported that the information that they received lead them to expect a negative prognosis and to worry about the possibility of a premature death, thus increasing the perception they had of CDG as a severe and potentially lethal disease.

Difficulties were also described regarding *barriers in accessing information* about the disease and not being able to have their main questions answered. The lack of knowledge about CDG of the assisting physicians did not allow these professionals to provide all the information needed, with parents reporting *difficulties in getting support and guidance* from them. Some parents reported feeling lost and insecure about the next steps after the diagnosis when health professionals showed lack of sensibility and availability to guide them in what to do. Some parents reported *difficulties in connecting with other CDG families*, feeling alone in their situation.

1.2.3. Sub-category – *Factors that promoted the acceptance of the diagnosis*

Participants reported several factors that supported them through the initial process of accepting and adapting to the diagnosis. *Perceiving the disease as less severe* than previously expected, or when compared to other diagnosis possibilities, helped parents through this period.

Participants reported receiving *support from other CDG families and CDG associations*, which allowed them to hear about the experience of other families and receive useful information. Support groups and associations were also reported as essential to put families in contact with CDG medical experts, a much-valued opportunity

for these families that had previously encountered health professionals not aware of the disease. *Support from health professionals* who were perceived as competent and experts regarding CDG lead family caregivers to feel more secure. Participants referred their *life partner* as the person with whom they lived all this difficult process while supporting each other. *Family members, friends and work peers* were also mentioned as a source of support.

2. Dimension – *Living with CDG in the family*

This dimension includes the categories *Participants' knowledge about the disease*, *Main changes*, *Demands and challenges*, *Main concerns*, *Resources that ease the experience of living with CDG*, *Coping strategies*, and *Positive experiences/outcomes*.

2.1. Category – *Participants' knowledge about the disease*

Table 5. *Sub-categories, codes, number of participants (%), and examples for the Category "Participants' knowledge about the disease".*

Sub-categories	Number of participants (%)	Examples of answers
General knowledge about CDG	40 (100%)	*"It's a very rare genetic disorder which impacts around 1000 children worldwide, there is no cure and it has motor and mental implications and these implications can vary from mild to extreme."*
Participants' will to know about CDG	18 (45%)	*"I would like to know what has to be done in terms of research and clinical trials so they can possible find cure."*
Difficulties in explaining to other people	4 (10%)	*I really struggle to explain the disease to other people because I feel most of the people does not have the medical knowledge to understand it."*

2.1.1. Sub-categories – *General knowledge about CDG*; *Participants' desire to know about CDG*; *Difficulties in explaining CDG to other people*

All the participants showed an overall adequate knowledge about CDG. They were aware it is a rare, genetic and metabolic disease, caused by defects in the process of glycosylation. They referred its multisystemic nature, reporting several of the main

symptoms. The fact that there is no available cure and that most subtypes have no effective treatments was also reported. Despite being aware of the main features of the disease, some participants mentioned *difficulties in explaining* such a complex disease *to other people* in a clear and simple way. Although parents felt comfortable about their understanding of CDG, they expressed *the wish to know more* about the possibility of future treatments or cure, the evolution of the disease in the specific case of their child, and which researchers are investigating.

2.2. Category – *Main changes*

Table 6. *Sub-categories, codes, number of participants (%), and examples for the Category "Main changes".*

Sub-categories	Codes	Number of participants (%)	Examples of answers
Family life	*Family dynamics and routines*	15 (37,5%)	*"We had to understand and adapt our life as a family which has a kid with a very severe disability."*
	Family's future projects	4 (10%)	*"We wanted to have another kid, but now we don't want anymore because it would be a huge burden."*
	Couple separation and divorce	2 (5%)	*"It affected a lot our couple in a bad way, we divorced."*
Instrumental changes	*Work life*	13 (32,5%)	*"I needed to find a part-time job in which I could work from home and it was very difficult."*
	Adaptation of the house or moving to a new one	6 (15%)	*"We had to do some changes in the house to make everything accessible for her."*
	Moving to another city	3 (7,5%)	*"We were living in another state that was not medical advanced like where we are now."*

2.2.1. Sub-category – *Family life*

Living with CDG affects all families and family members reported several important changes in their lives. Global changes in *family dynamics and routines* were the most often reported, concerning changes in the role each parent plays or the relation

with the other children. The need to give up *future projects*, such as having more children, or in some cases getting *divorced or separated* due to the demands of the disease were also reported.

2.2.2. Sub-category – *Instrumental changes*

Many parents reported the need to make changes in their *work life*, with one of the parents having to reduce the working hours or even to stop working to care for the patient. Some families had to *adapt their house or move to a new one* due to the physical limitations of the patient, or even *moving to another city* to access better medical support.

2.3. Category - *Demands and challenges*

Participants identified demands and challenges brought about by the disease for themselves, for the whole family and for the patient him/herself.

Table 7. *Sub-categories, codes, number of participants (%), and examples for the Category "Demands and challenges".*

Sub-categories	Codes	Number of participants (%)	Examples of answers
For the participant	Being the expert on CDG	20 (50%)	*"I know much more about CDG than them, they never tell me something I don't know already."*
	Difficulties in emotional regulation	19 (47,5%)	*"Emotionally, to deal with CDG feels like a rollercoaster. Sometimes I accept what we have and am proud of him, other times something small happens and I just break down crying."*
	Health professionals' lack of knowledge about CDG	19 (47,5%)	*"Most of the info I have is from the CDG networking and it is that info I print and take to the doctors because they don't know her disease."*
	Functional limitations of the patient	15 (37,5%)	*"What may be more difficult is the time we have to take to do every single thing with her, because she can't do it alone so she needs our help."*

Not being offered psychological support	10 (25%)	*"There was no psychological help, and we started to feel really bad."*
Lack of social support and social life	10 (25%)	*"I don't have help, it is just me and her."*
Role as carer	8 (20%)	*"Her illness is very demanding, she is my full-time job."*
Difficulties in obtaining health care	6 (15%)	*"I don't trust the medical team and this is the problem because during a lot of time she didn't have neurological follow-up at all because nobody wanted to take care of her because they didn't understand what was happening."*
Transition from pediatric to adult care	6 (15%)	*"Now she has more doctors from different specialties, before it was more centralized in the same service. The transition was a bit difficult."*
Impact on other family members	5 (12,5%)	*"What is more difficult is to see the impact of stress my mom has to be a carer all the time, this is hardest thing." (a sibling)*
Parenting the patient	5 (12,5%)	*"He has some compliance issues in general, so it's hard to make him do the things he needs to do."*
Physical exhaustion	5 (12,5%)	*"We are very tired all the time, physically tired."*
Management of appointments, therapies and treatments	5 (12,5%)	*"I find very hard and stressful to manage all the appointments."*
Difficulties in being trusted by health professionals	5 (12,5%)	*"There is a difficulty of the doctors to accept that in front of them there are family members who have more knowledge about the disease than they do."*
Accepting the disease	3 (7,5%)	*"I am still very upset with CDG, I don't like CDG, I don't accept it."*
Lack of information	3 (7,5%)	*"There are still a lot of his disease that I don't know because there is not research yet."*

For the family	Financial burden	11 (27,5%)	*"Financially it has been more difficult because we spend a lot of money with her therapies."*
	Lack of social support	10 (25%)	*"Besides us there is nobody to take care of her."*
	Life and family management	7 (17,5%)	*"He needs some care all the time, so it is challenging sometimes in terms of the routines, to manage everything between us."*
	Need to travel long distances to access health care	7 (17,5%)	*"There is a small hospital next to our house but it is not prepared to take care of more complicated things so we need to go to the central one which takes about 1 hour to go there."*
	Need to care for and supervise the patient most of the time	6 (15%)	*"Our lives were only focused on him so we organized ourselves to have always someone with an eye on him."*
	Management of the couple relationship	5 (12,5%)	*"In the beginning, with the stress, lack of sleep, fears, we had some problems in the couple relationship but now it is better."*
	Anticipation of risks in the daily life	3 (7,5%)	*"Every single thing, even the small things, has to be thought beforehand."*
	Psychological support as a burden in life management	2 (5%)	*"No, psychological guidance was offered but it was one more appointment to go and we were full of it."*
For the patient	Functional limitations	32 (80%)	*"We see it is a challenge for him to make himself understood and more independent in the daily routines and he can't."*
	Difficulties in social relationships	15 (37,5%)	*"She is becoming aware of her reality and she expresses it, she says she is different from the kids of her age."*

2.3.1. Sub-category – *For the participant*

Participants reported feeling the need to assume most responsibilities in the healthcare process, such as assuring that the exams and follow-up are done properly, *being the experts on the disease* instead of health professionals. The *health providers' lack of knowledge concerning CDG* was perceived as challenging, mostly when *parents did not felt recognized as credible informants and their experience was not taken in account*. The *management of medical appointments and every task related with health care* was also described as very demanding. *Difficulties in accessing the necessary health care services*, mostly when going to the urgencies, and the change *from a pediatric care to adult care* were also mentioned.

Parents also mentioned difficulties in *regulating their negative emotions* related to the several demands imposed by the disease. Fear and constant worry regarding uncertainty about the future, stress and anxiety and intense feelings of sadness, are described as overwhelming and always changing, as a "*rollercoaster*" of feelings, difficult to control. Most parents referred they were *not offered psychological support*, which they would value.

Parents' *role as carers* was reported as physically and emotionally demanding, with this new identity largely taking the place of their previous role as a parent. This was related to the continuous need for assistance of patients with important *functional limitations. Physical exhaustion* was mentioned, too.

Within the family, parents are most of the time the only ones caring for the patient, reporting *lack of social support* from other family members or other people, which ends up impacting their *social life*. Other challenges reported by caregivers were trying to minimize the *impact of the disease on the other family members*, mainly on the spouse and on healthy siblings; specific activities of *parenting the patient*; *accepting the disease*; and *lack of information*.

2.3.2. Sub-category – *For the family*

Considering the challenges brought about by the disease for the whole family, participants mentioned the *family life and time management*, and specifically the *management of the couple relationship.* Although several considered the possibility of

searching for *psychological support*, or accepting it when offered, this was also perceived as another *burden in their life management*.

Financial hardship was reported by several participants, mostly due to the costs related to health care, lack of insurance and having just one parent as the sole provider. Parents also reported *lack of social support* and feeling much alone in caring for the patient. The *need to travel long distances to access expert medical support*, and the *need of constantly supervising and caring for the patient* were mentioned by some participants. Being alert and always *anticipating the many possible risks* for the patient was reported as stressful.

2.3.3. Sub-category – *For the patient*

Parents considered that the main challenges for the patient were his/her own *functional limitations* due to the disease, such as motor impairments, balance and coordination, and speech difficulties, with some family caregivers reporting the patient's frustration with these limitations. On the other hand, some parents also reported difficulties for the patients with the integration in school (either regular or special needs schools), where peers may have different abilities and competencies, and staff tends to be overprotective of them. This brings about *difficulties in social relationships* and sometimes an awareness of own limitations resulting in frustration or low self-efficacy.

2.4. Category – *Main concerns*

Participants reported concerns regarding both their present life and their future.

Table 8. *Sub-categories, codes, number of participants (%), and examples for the Category "Main concerns".*

Sub-categories	Codes	Number of participants (%)	Examples of answers
Concerns regarding the present	Development and autonomy of the patient	14 (35%)	*"I am very focused on her motor and cognitive skills. I really want her to walk and to talk. We want to make her the most autonomous possible."*

Disease and health in general	13 (32,5%)	*"That he gets sick, because if he has a fever he can have seizures. When he gets sick it's a huge concern."*
Patient's adaptation to school and acquirement of academic competencies	8 (20%)	*"For the school, I think it will be ok but I am aware there will be some difficulties."*
Lack of control in protecting the patient	7 (17,5%)	*"We let him do more and more things but we are most of the time afraid that he may fall."*
Lack of control in disease management	6 (15%)	*"I'm afraid he can get sick and there won't be anybody who knows what to do with him."*
Social integration of the patient	4 (10%)	*"That he can socialize better."*
Attention given to siblings and including them in the process	4 (10%)	*"We take (the patient's sibling) to all the appointments to make sure she is part of all the process."*
Burden of care for the main caregiver	3 (7,5%)	*"I am concerned about how it affects their life and the life of my mom that has to do efforts every day." (a sibling)*
Other caregivers' ability to take care of the patient	2 (5%)	*"I have a number I need to call to get some help at home, but my fear is that someone is going to hurt her. I have to try to find the best person."*
Family routines	2 (5%)	*"We need also to reorganize its schedule to facilitate the family management and make it simple."*
Better medical support	2 (5%)	*"We are considering that one day we have to move to where there is more access to health assistance and where there are people knowing about CDG."*
One's competency	1 (2,5%)	*"I'm less dynamic and I'm wondering how I could manage the situation."*
One's wellbeing	1 (2,5%)	*"If I am more tired I am not so available for the kids, I need to be mentally available for them."*

	Financial concerns	1 (2,5%)	*"Financial issues are a concern too, because it is a huge burden we have nowadays."*
	Adaptation of physical structures	1 (2,5%)	*"We need to find a house more adapted and with only one floor because it's a huge problem, he is heavy and I need help to take him to his room, so when I am alone I can't."*
	Patient's behavior	1 (2,5%)	*"We are concerned we can't manage his compliance issues because it is a huge challenge to make him comply with something."*
	Patient's routines	1 (2,5%)	*"To get him out so he doesn't spend most of the time inside the house."*
Concerns regarding the future	Parents' future death	9 (22,5%)	*"Something that concerns us is what is going to happen to her when we won't be here for her."*
	Growing old and needing to go on caring for the patient	8 (20%)	*"I am concerned about the time my parents will be older, what is going to happen to her, because I will have to take care of her and I feel it is too much for me." (a sibling)*
	Future of the patients as an adult	7 (17,5%)	*"We would like to know how we can prepare her for adult life as a CDG patient, what can we do as parents to help her in adult life."*
	Uncertainty of the future of the patient	6 (15%)	*"Not knowing what will happen in the future is a concern."*
	Evolution of the disease	3 (7,5%)	*"My worry now is how the disease will develop over time when she grows up"*

2.4.1. Sub-category – *Concerns regarding the present*

The current concerns most reported were related with the *development and autonomy of the patient*, with participants reporting their aim to stimulate the patient's development as much as possible, thus recurring to various adjuvant therapies. Parents were especially concerned with their child being able to walk and talk, thus acquiring some level of independence in daily tasks.

The *disease and the patients' health in general* were also identified as a concern, related to the parents' feeling of neither being able to fully *control the disease* that has no effective treatments and cure, and is sometimes marked by unpredictable symptoms, nor to *protect the patient* from the risk of falls and accidents. *Adaptation to school and acquiring of academic competencies*, and the *social integration of the patient* who at some point starts to be aware of his/her limitations, were other topics mentioned by participants. Parents also identified concerns related to the patient and the whole family such as the need to balance time and *attention given* to the patient and *the siblings, and how to include the siblings in the care of the patient*; concerns with the *burden of care for the main caregiver*; concerns with *other carers'* (teachers, social workers) *ability to effectively attend the patient* and in who parents can trust; the *family routines* and how to better manage family's schedules, and *financial concerns*. A few participants reported concerns regarding the need to find *better medical support* when the family is not followed by a health team in who they trust and with a minimum knowledge of CDG; the *competency* and *well-being* of the participant to maintain the care and a balanced life routine; the *adaptation of physical structures* due to the patient's motor impairments; the *patient's behavior* problems; and the *patient's routines*.

2.4.2. Sub-category – *Concerns regarding the future*

Regarding the future, parents' main concerns regarded the anticipation of their *future death* or inability *to care for the patient when as they get older*, with some siblings mentioning being worried about the the need for them to assume the care of the patient in the future. Other parents are concerned with the *future management of the daily life of the patient as an adult*, regarding health, social and educational/professional adult facilities; others express concerns with the global *uncertainty with the future of the patient*, and the *evolution of the disease*.

2.4.3. Comparing concerns of participants according to the patients age group

Concerns of participants varied according to the patient being a child, an adolescent or an adult. Family caregivers of children showed concerns more focused on the present, mostly related with stimulating the *development and autonomy of the patient*, the management of the *disease and health in general*, and the *patient's adaptation to*

school and his/her acquirement of academic skills. The most reported concern regarding the future was related to the *uncertainty of the future of the patient*.

Family caregivers of adolescents were more concerned with the patients' future than with the present. Their main concerns were the *future of the patient as an adult*, their *own aging and decreased ability to care for the patient*, and the *anticipation of their death*. Regarding the present, concerns were related to the need to find a *balance between caring for the patient and for the other children*, and concerns about *their lack of control to fully protect the patient*.

Family caregivers of adult patients reported more present focused concerns, namely with the patients' *disease and health in general* and with their *lack of control to protect the patient*. The *anticipation of their future aging and absence* were the most reported concerns regarding the future.

2.5. Category – *Resources that ease the experience of living with CDG*

Table 9. *Sub-categories, codes, number of participants (%), and examples for the Category "Resources that ease the experience of living with CDG".*

Sub-categories	Codes	Number of participants (%)	Examples of answers
Social support	Family, friends and work peers	25 (62,5%)	*"I have some social support that helps me to have a better emotional stability, they don't let me get in a deep sadness, I can share my emotions with them and they do the same with me and this is fundamental."*
	CDG families and associations	23 (57,5%)	*"To have contact with other families helps me to deal with the daily life hassles. It is a big help when we share experiences."*
	Private carers	15 (37,5%)	*"We have a babysitter who is a nurse student that keep an eye on him and is prepared in case of a health issue, so she takes good care of him."*
	Life partner	13 (32,5%)	*"My husband is wonderful because he always says that she (our daughter) can do it and finds a way for it."*

Patient and caregiver as resources		27 (67,5%)	*"We are blessed she got until here so great and it makes coping with the daily life a bit easier."* *"The communication I have with her is really strong. She is so happy and that gives us a huge strength and motivation to continue, she is special and unique."*
Health support	Good relationship with health professionals	25 (62,5%)	*"I have been having a really good experience with the medical team. They listen to us, they answer our doubts, they have time for us, they know how to help us, they are patient, they give us tips to better organize our lives. They try to understand what we need and help us getting that. They are involved with the parents, they don't limit themselves to do just their work, we can count with them and that is really important."*
	Psychological support	10 (25%)	*"We did have some counselling to get help coping with the situation after the final diagnosis. It helped us because we got a new perspective about the feeling we were having."*
Educational and therapeutic activities		22 (55%)	*"He likes the therapies because he likes to play with the therapist so he doesn't realize it is a work he needs to do."*
Financial support		9 (22,5%)	*"Financially we have managed it, because we have some support from the state and our insurance."*

2.5.1. Sub-category – *Social support*

When asked about what or who helped them to manage their daily life and supported them through their adaptation to the disease, different forms of social support were reported. *Family members, friends and work peers* as well as the *life partner* were reported as the most helpful source of support when dealing with life demands. *Other CDG families and CDG associations* were considered as very helpful too. Some family members could have *private carers*, such as private teachers and babysitters that ease the management of daily routines.

2.5.2. Sub-category – *Patient and caregiver as resources*

Several parents reported the *patient himself* as one of the main source of support. Patients' improvements and positive development, their motivation to try and do new things, and the fact that they were perceived as mostly joyful and content, giving back much affect, helps parents to better cope with the disease.

Two mothers regarded their *own personal characteristics* of calm, flexibility, as some important resources.

2.5.3. Sub-category – *Health support*

Having a *good relationship* with sensible and supportive *health team*, in whom parents can trust, who take the parents' opinion in consideration, help parents to better adapt to the daily demands. A few participants and patients had the possibility of receiving *psychological intervention* and this was also reported as useful.

2.5.4. Sub-categories – *Educational and therapeutic activities*; and *Financial support*

Participants mentioned other important sources of support such as the various *educational and therapeutic activities* provided to the patient, which play a role of resource due to the improvements patients take from it, and to the professionals' care and support. State *financial support* and benefices were reported as attenuating the family hardships.

2.6. Category - Coping strategies

When going through such a demanding and difficult process of daily adaptation to a rare disease, families need to develop diversified coping strategies. Participants described a large variety of coping strategies, both emotion focused and problem-focused as described in Table 10.

Table 10. *Sub-categories, codes, number of participants (%), and examples for the Category "Coping strategies".*

Sub-categories	Codes	Number of participants (%)	Examples of answers
Emotion-focused strategies	Normalization	12 (30%)	*"We deal with her in the most normal way so she won't be completely dependent of us. We let her play alone, move around the house, she plays with her siblings; they go very well with each other."*
	Minimization	10 (25%)	*"She may need help for some things, but she also doesn't need help with things that some people need help for, like doing friends for example."*
	Spirituality, Religion and Hope	8 (20%)	*"Faith is something that motivates me a lot and in which I get support for me. I think all of us have a mission and maybe mine is this one. It helps me to get a meaning to all of this."*
	Positive thinking	7 (17,5%)	*"I am sure she will improve if everyone continues to stimulate her. It may take time but she will make it."*
	Positive re-evaluation	6 (15%)	*"Every morning I look at myself in the mirror and I think: with two legs, two arms and a brain I can do whatever I want."*
	Acceptance by emphasizing the positive aspects of the situation	4 (10%)	*"But day by day we were noticing she was not in a life danger, so we started to manage the situation and focus in being happy with what we had."*

	Avoidance	2 (5%)	*"I just try not to think about it to go on with my day."*
	Wishful thinking	2 (5%)	*"She is so young yet, with time it will appear something to treat her."*
Problem-focused strategies	Active coping by planning and problem solving	16 (40%)	*"We try to make her speak actively with other people to practice more, like get her ordering in restaurants."*
	Search for new information and learning of new competencies	12 (30%)	*"I try to specialize myself as much as I can."*
	Searching for balance	12 (30%)	*"We try to do it in balanced way, but we try to make time for each other because if we don't do that we are not happy. We spend time alone and talk."*
	Search for sources of social support	9 (22,5%)	*"I talked with my friends at that moment and it helped me to deal with the situation."*

Participants reported a balanced use problem-focused and emotion-focused strategies, although the first ones were more diversified-strategies.

Among the most used problem-focused strategies were *active coping by planning and problem solving* to promote the patient's autonomy and quality of life, by taking him/her to different therapies and by stimulating him/her to be autonomous in daily tasks, such as dressing or eating alone; *searching for new information and learning new competencies*, to better manage the disease and its consequences; and *searching for balance in life* between the multiple roles they play, both as an individual (parent, spouse, worker) and carer. This last strategy differs from the active coping by planning and problem solving since it mainly involves planning and organization of family's life, and not the resolution of the situation itself.

We identified several emotion-focused strategies such as *normalization*, the most reported one, as an effort to maintain family routines and valuing the normal aspects of the family's and the patient's life and; *minimization* of the implications of the disease; relying on *spirituality, religion and hope*; and *positive thinking.*

2.7. Category - *Positive experiences/outcomes*

Although CDG clearly impacts negatively families, many participants reported positive outcomes from their lived experience with this rare disease.

Table 11. *Sub-categories, codes, number of participants (%), and examples for the Category "Positive experiences/outcomes".*

Sub-categories	Codes	Number of participants (%)	Examples of answers
For the participant	Improved self-perception	21 (52,5%)	*"I am a more conscious person, more accepting of disability, more patient. It also made me a better person."*
	Personal and professional development	4 (10%)	*"The experience with him and spending so much time in the hospitals influenced me to get a career in health."*
For the family	Family's development	10 (25%)	*"We are very close and we have a very strong sense of family."*
	Siblings	7 (17,5%)	*"My oldest son got more empathic and understanding since he was very young, by experiencing our lives with his CDG sibling."*
	Stronger social network	4 (10%)	*"Some other friends stood up by us, said that they loved us and that they knew we were struggling and wanted to help us."*

2.7.1. Sub-category – *For the participant*

Most of the participants reported positive impacts on their own functioning as individuals (*self-perception*). They referred to themselves as "*better persons*", with more resilience, patience, compassion and empathy, and as facing disability more consciously. Daily life challenges related to the disease made them realize they are stronger than they previously thought, and that they can deal adequately with hard challenges. Some family members reported having a job or career linked with the health field due to their experience with the patient, which motivated them to get more interest for this area (*personal and professional development*).

2.7.2. Sub-category – *For the family*

Some participants reported that the family experience of living with a patient with CDG brought family members together and closer to each other. A "*new way of life*", living without haste, and with a more positive perspective about life, valuing small moments and experiences and relativizing others as not so important (*family's development*). Some parents referred a *positive impact on the healthy siblings*, who grew up inspired by the motivation of the patient, and made them "*better people*", with more "*compassion*", "*patience*" and "*empathy*". The siblings themselves also recognized having more responsibilities and maturity from a young age, and being more "*sensitive*" to the needs of other people with disabilities. Another positive outcome was the *strengthened social support network* of friends and family.

3. Dimension – *Messages for other families*

Table 12. *Codes, number of participants (%), and examples for the Dimension "Messages to other families".*

Codes	Number of participants (%)	Examples of answers
Importance of searching for social support	13 (32,5%)	*"Ask for all the help you need, to family, friends, doctors, because the first times are complicated."*
It is important to have trust and hope for the future	11 (27,5%)	*"To have hope, don't give up."*
Importance of searching for information and select the most relevant for each case	11 (27,5%)	*"It's important to do a selection of the information you search."*
To put the focus on the patient well-being	9 (22,5%)	*"Continue to support your child, give him every opportunity to improve, take him to therapies because it helps him to improve."*
Happiness is possible	8 (20%)	*"It can be hard, but happiness is possible, there are some things that need to be adapted but happy moments are possible."*
Look at our experience	7 (17,5%)	*"I would try to make them not go through the same things I had to pass, giving my example."*

To accept one's own negative emotions	6 (15%)	*"It's ok to be sad and to think that the world is an awful place."*
To adapt expectations because each patient is unique	5 (12,5%)	*"We need to have a balance when comparing with other kids because every kid is unique and they are so different even if they have the same type of CDG."*
It is difficult but it gets easier overtime	5 (12,5%)	*"It will take time to fully understand the illness and accept the diagnosis but it gets easier over time."*
With time, thing may change	2 (5%)	*"Don't make plans, some things are going to change."*
To accept the disease as part of life	2 (5%)	*"Allow yourself to accept it and incorporate it into your life, it will influence the happiness of your child."*

At the end of the interviews, participants were asked about what they would like to say to a family recently diagnosed with CDG. They referred they would advise families to *search for social support* from family, friends, psychologists, but mainly from other CDG families and associations, that were described to be the most helpful support and source of information families could get. Another advice was to *search for information*, although they mentioned the importance of selecting the information. They called attention for the importance to *focus on the patient's well-being* and to *be aware that each patient is different* when comparing him/her to other patients, being important to *adapt expectations.* Participants mentioned that it could be useful to *share their experiences as CDG families* and highlight the *main possible changes during the adaptation process.* They alerted the new parents to be aware that the *beginning is the most difficult part but that it gets easier with time*, and that is *possible to find happiness, while accepting the disease* and each one *own negative emotions.* Overall, they wanted to convey a message of *trust, hope and faith.*

4. The perspective of grandmothers and siblings

The majority of participants in this study were mothers and some were fathers. Given the diversity of the individual situation of each participant and the variety of the individual experiences reported by each participant, it is not possible to establish any comparison.

We also interviewed two grandmothers that assisted the parents in caring for the patient, and five adolescent and adult siblings. Grandmothers expressed many ideas similar to those reported by the parents regarding their emotions, concerns and challenges. However, the coping strategies identified by them were almost exclusively emotion-focused, differently from the parents, who also reported problem-focused strategies.

As expected, siblings described a somehow different perspective about their lives with a CDG patient, although also many of their verbalizations were similar to those of the parents. The main specificities of their experiences were related to their concerns with the impact of the disease on the parents and mainly on the main family caregiver (usually the mothers), and their worries regarding the future of the patient, the evolution of the disease and their own need to assume the responsibilities of caring for the patient in the future when parents will not be capable to do it. They were able to see some positive consequences of the adaptation to the illness to the quality of their family life and three of them described these experience as having had some impact in their choice of a health-related profession.

DISCUSSION

The interviews with different family members involved in the care of the patient allowed to identify several categories regarding the experience of living with a CDG patient. These are related to the burden experienced, to the psychological impact on family caregivers and to the ways of coping with the daily demands imposed by the illness. Although there were much similarities in the reports of family members, we also found many differences in individual experiences, according to the kinship with the patient, the age group of the patient, his/her type of CDG, the type of the diagnosis, and the country of residence of the family, among other individual characteristics, which influenced the experience of living with this rare health condition.

Participants reported that caring for a CDG patient had physical and psychological/emotional health implications, especially for parents who assume the main responsibilities of care. Since the moment they knew about their child disease, and as shown in previous literature, their role as individuals change to integrate the role of main health carers (Kepreotes et al., 2010). Receiving the diagnosis is reported as a strong emotional experience that parents easily recall in detail (Havermans et al., 2015), describing feelings of anxiety, sadness, shock, anger or denial, but also some relief for finally receiving a correct diagnosis (Pelentsov, Laws, et al., 2015). Experience of strong and constant negative emotions is not restricted to this period. In our study, stress, anxiety, and deep feelings of sadness were described as difficult to manage, as in previous studies with caregivers of rare health conditions' patients (Dogba et al., 2014; Gallop et al., 2009; Kim et al., 2010; Lipinski et al., 2006; Senger et al., 2016; Weng et al., 2012). As in CDG, the diseases reported in these studies are characterized by symptoms such as physical disability, neurological manifestations and developmental delays.

Literature as shown, and we observed in our results, that families with patients with serious health conditions experience a heavy financial hardship, due to the costs of health care, lack of insurance, and expensive and specialized treatments, therapies and equipment (Coad et al., 2015; Pelentsov et al., 2016; Zurynski et al., 2008).

In our study, participants reported current concerns mostly related to the development and autonomy of the patient and with the disease and health well-being. Most caregivers enroll in daily efforts to make their children progress, involving them in multiple therapies and experimental studies, and practicing with them at home trying to

make them achieve some degree of autonomy in daily tasks. This concern seems particular to this population, since other studies reported caregivers' concerns more related with their child's acceptance of the disease and of his/her personal difficulties due to the disease (Moreno García et al., 2008) and management of a normal family life (Coffey, 2006), and not so much this struggle to help them overcome their limitations. It is important to highlight that participants also reported worries and fear about the consequences of their future death to the care of the patient, and for the siblings, who also reported concerns about the need to assume the future care of the patient when parents will not be capable to do it or after their death. Moreno García and colaborators (2008) also found similar parents' concerns. It should be noted that the impact of the disease on siblings is not restricted to this anticipated future when parents will not be present, but during the whole experience of living with a rare disease within the family (Pelentsov, Fielder, et al., 2015; Pelentsov, Laws, et al., 2015).

The difficulties in accessing health care and support was identified by some participants as a challenge heavily contributing to the burden experienced. Health professionals' lack of knowledge and experience about CDG was found to be difficult, not only during the diagnosis period but also in supporting their daily management of the disease. A recent study with Australian families showed that health professionals do not have the training to easily recognize symptoms of rare diseases (Zurynski et al., 2017). This ends up delaying the diagnosis, with families consulting multiple physicians, going to different health centers and having their child doing multiple and sometimes unnecessary medical screenings (Anderson et al., 2013; Weng et al., 2012). Some of our participants reported that this lack of professional support forced them to assume the role of "experts", which was voiced as extremely stressful and overwhelming for them. Parents feel forced to lead tasks such as developing expert knowledge about the disease and being constantly updated about available information, managing appointments, treatments and therapies, and making most of the important decisions concerning their child health care, taking all the responsibility for the disease management (Pelentsov, Fielder, et al., 2015; Pelentsov et al., 2016). However, several families in our study are followed by a multidisciplinary health team and find their relationship with their team to be good. Having a good relationship with a sensible and supportive health team, in whom the parents can trust, and who take the parents' opinion in consideration, is an important support for parents in their adaptation to the daily demands (Graungaard & Skov, 2007).

Participants identified several resources available to support them in dealing with the challenges and difficulties of the illness. Social support was the most helpful resource reported with family members, through friends and work peers. For some the life partner was the most important source of support. The burden experienced by these families can be eased when they can count on the support from family, friends, health and social services, and families in similar situations (Dogba et al., 2014; Read, 2003).

In our study, CDG families and CDG associations were frequently reported as an extremely helpful support throughout participants' lived experience with this rare disease. The opportunity to meet people with similar life conditions and to know other families' experiences was described as one of the best resources in coping with the illness demands. Support from families in similar conditions seems important for caregivers of patients' with rare health conditions (Grut et al., 2008). Hearing and sharing experiences help caregivers not to feel so alone in their situation and to access more accurate information about the disease. In previous studies, this is reported by parents as an helpful factor when coping with daily challenges (Bogart et al., 2017; Glenn, 2015; Pelentsov, Laws, et al., 2015). It gives parents a sense of belonging, decreases their stress and empowers them to manage their life situation imposed by their child's disease (Coad et al., 2015; Mathiesen et al., 2012; Shilling et al., 2013).

Another important resource for our participants was the patient himself, specifically the possibility of observing his wellbeing, his improvement and progress, and his motivation to overcome limitations. Paster and colaborators (2009), in a study with children with disabilities, also found that patients themselves were seen by the family members as a source of motivation and strength.

Coping strategies described by participants were diversified according to the specific situation and the specific challenges faced by each family member. Individual characteristics of the person, the situation within the family and the specific features of the disease are known to influence the way family members cope (Dellve et al., 2006). In our study, problem-focused strategies such as active coping and searching for information and learning new competencies, and emotion-focused strategies as normalization and searching for balance in life were among the most frequent. Family caregivers of children with inherited metabolic diseases, like CDG, reported using active coping strategies, but also future-orientated thinking (Siddiq et al., 2016), which we did not find in our results. A study conducted with caregivers of children with a rare genetic

disorder found internet to be an useful resource for them, who reported using it to search information about the disease, which helped them decrease their levels of stress (Gundersen, 2011). Normalization has shown to allow parents of children with serious health conditions to keep their life going in a balanced way, while managing daily demands (Atkin & Ahmad, 2000), and is also perceived as a positive motivation for families (Knafl et al., 2010).

CONCLUSION

This qualitative study aimed to better understand and highlight family members' experiences of living with a CDG patient, considering their different and specific perspectives. Most of the research has been focused on the affected individual, with little recognition of the burden faced by the main caregivers. To our knowledge this is the first study to explore the specific impact of CDG on caregivers. This may probably be due to the rarity of this disease, but it is important to recognize the burden experienced by these families, the psychological impact of the illness and the ways caregivers use to cope with the demands imposed by the disease, in order to raise hypothesis about the best strategies to assist and support them.

Aside to the strengths of this study, some important limitations should be recognized. Our study is restricted to a single disease, like most of the literature discussing families with children with a rare condition. The sample was sourced with the help of an international association, however the very demanding lives of this population prevented their participation in the study, even if they wished to. Our sample was small and much diversified. Among parents, we interviewed mostly mothers, although having the perspectives of more fathers could have provided a richer description of the impact of the patient's condition on the family as a whole. Most of the interviews were conducted in the native language of the participants, however in some cases this was not possible, and may have hindered the spontaneity of the reports. Also, some couples were interviewed together, which may have led to one of the members expressing less openly his/her ideas. Our sample was geographically dispersed, and there were important differences identified concerning cultural context and resources available in the different countries; however, these were not explored in-depth.

The main findings of the present study highlight the importance for these families to access specialized health professionals and updated information in the field of rare diseases. Health professionals play a critical role in supporting these families and need to understand the caregivers' experience of the illness-related stressors and unmet needs, to better assist them in their role. Health providers need to value the caregivers' perspectives about the care of the patient. Given the demands and burden experienced by these families, psychological support should be prioritized and offered at an early stage, and not only during the most critical times. Family caregivers could benefit from effective

interventions aiming not only at teaching them to manage their child's disease, but also to support them in the management of their stress and negative emotions (Moreno García et al., 2008). Providing adequate professional support and increasing the knowledge and skills of family caregivers of patients with rare health conditions can facilitate the coping processes and reduce their stress. Improving their coping skills will help them to more effectively take advantage of the resources available (Atkin & Ahmad, 2000; Dellve et al., 2006). Besides, it will ease parental adaptation the balanced use of strategies focused on emotional regulation and of strategies more focused on daily life demands (Santos & Barros, 2015).

REFERENCES

Anderson, M., Elliott, E. J., & Zurynski, Y. (2013). Australian families living with rare disease: experiences of diagnosis, health services use and needs for psychosocial support. *Orphanet Journal of Rare Diseases*, *8*(1), 1. https://doi.org/10.1186/1750-1172-8-22

Atkin, K., & Ahmad, W. I. U. (2000). Family care-giving and chronic illness: how parents cope with a child with a sickle cell disorder or thalassaemia. *Health & Social Care in the Community*, *8*(1), 57–69. https://doi.org/hsc211 [pii]

Aubeeluck, A. V., Buchanan, H., & Stupple, E. J. N. (2012). "All the burden on all the carers": Exploring quality of life with family caregivers of Huntington's disease patients. *Quality of Life Research*, *21*(8), 1425–1435. https://doi.org/10.1007/s11136-011-0062-x

Aymé, S., & Schmidtke, J. (2007). Networking for rare diseases: A necessity for Europe. *Bundesgesundheitsblatt - Gesundheitsforschung - Gesundheitsschutz*, *50*(12), 1477–1483. https://doi.org/10.1007/s00103-007-0381-9

Bellgard, M., Beroud, C., Parkinson, K., Harris, T., Ayme, S., Baynam, G., … Hunter, A. (2013). Dispelling myths about rare disease registry system development. *Source Code for Biology and Medicine*, *8*(1), 21. https://doi.org/10.1186/1751-0473-8-21

Berge, J. M., Patterson, J. M., & Rueter, M. (2006). Marital satisfaction and mental health of couples with children with chronic health conditions. *Families, Systems, & Health*, *24*(3), 267–285. https://doi.org/10.1037/1091-7527.24.3.267

Bogart, K. R., Frandrup, E., Locke, T., Thompson, H., Weber, N., Yates, J., … Breaker, A. R. H. (2017). "Rare place where I feel normal": Perceptions of a social support conference among parents of and people with Moebius syndrome. *Research in Developmental Disabilities*, *64*(February), 143–151. https://doi.org/10.1016/j.ridd.2017.03.014

Boyer, F., Drame, M., Morrone, I., & Novella, J. L. (2006). Factors relating to carer burden for families of persons with muscular dystrophy. *Journal of Rehabilitation Medicine*, *38*(5), 309–315. https://doi.org/10.1080/16501970600731578

Braun, V., & Clarke, V. (2006). Using thematic analysis in psychology. *Qualitative*

Research in Psychology, *3*(2), 77–101. https://doi.org/http://dx.doi.org/10.1191/1478088706qp063oa

Bruns, D., & Foerster, K. (2011). "We"ve been through it all together': Supports for parents with children with rare trisomy conditions. *Journal of Intellectual Disability Research*, *55*(4), 361–369. https://doi.org/10.1111/j.1365-2788.2010.01381.x

Case-Smith, J. (2004). Parenting a child with a chronic medical condition. *American Journal of Occupational Therapy*, *58*(2), 551–560. https://doi.org/doi:10.5014/ajot.58.5.551

Coad, J., Kaur, J., Ashley, N., Owens, C., Hunt, A., Chambers, L., & Brown, E. (2015). Exploring the Perceived Met and Unmet Need of Life-Limited Children, Young People and Families. *Journal of Pediatric Nursing*, *30*(1), 45–53. https://doi.org/10.1016/j.pedn.2014.09.007

Coffey, J. S. (2006). Parenting a child with chronic illness: a metasynthesis. *Pediatric Nursing*, *32*(1), 51–59.

Cohen, M. S. (1999). Families coping with childhood chronic illness: A research review. *Families, Systems, & Health*, *17*(2), 149–164.

Cousino, M. K., & Hazen, R. A. (2013). Parenting Stress Among Caregivers of Children With Chronic Illness : A Systematic Review. *Journal of Pediatric Psychology*, *38*(8), 809–828. https://doi.org/10.1093/jpepsy/jst049

de Lonlay, P., & Seta, N. (2009). The clinical spectrum of phosphomannose isomerase deficiency, with an evaluation of mannose treatment for CDG-Ib. *Biochimica et Biophysica Acta - Molecular Basis of Disease*, *1792*(9), 841–843. https://doi.org/10.1016/j.bbadis.2008.11.012

de Lonlay, P., Seta, N., Barrot, S., Chabrol, B., Drouin, V., Gabriel, B. M., … Cormier-Daire, V. (2001). A broad spectrum of clinical presentations in congenital disorders of glycosylation I: a series of 26 cases. *Journal of Medical Genetics*, *38*(1), 14–9. https://doi.org/10.1136/jmg.38.1.14

Dellve, L., Samuelsson, L., Tallborn, A., Fasth, A., & Hallberg, L. R.-M. (2006). Stress and well-being among parents of children with rare diseases: a porspective intervention study. *Journal of Advanced Nursing*, *53*(4), 292–402.

https://doi.org/10.1111/j.1365-2648.2006.03736.x

Dodge, J. A., Chigladze, T., Donadieu, J., Grossman, Z., Ramos, F., Serlicorni, A., … Wierzba, J. (2011). The importance of rare diseases: from the gene to society. *Archives of Disease in Childhood*, *96*(9), 791–2. https://doi.org/10.1136/adc.2010.193664

Dogba, M. J., Rauch, F., Douglas, E., & Bedos, C. (2014). Impact of three genetic musculoskeletal diseases: a comparative synthesis of achondroplasia, Duchenne muscular dystrophy and osteogenesis imperfecta. *Health and Quality of Life Outcomes*, *12*(1), 151. https://doi.org/10.1186/s12955-014-0151-y

Dulary, E., Potelle, S., Legrand, D., & Foulquier, F. (2017). TMEM165 deficiencies in Congenital Disorders of Glycosylation type II (CDG-II): Clues and evidences for roles of the protein in Golgi functions and ion homeostasis. *Tissue and Cell*, *49*(2), 150–156. https://doi.org/10.1016/j.tice.2016.06.006

Eklund, E. A., & Freeze, H. H. (2006). The Congenital Disorders of Glycosylation: A Multifaceted Group of Syndromes. *NeuroRx*, *3*(2), 254–263. https://doi.org/10.1016/j.nurx.2006.01.012

Eurordis. (2009). What is a rare disease? Retrieved January 30, 2017, from http://www.eurordis.org/content/what-rare-disease

Feltmate, K., Janiszewski, P. M., Gingerich, S., & Cloutier, M. (2015). Delayed access to treatments for rare diseases: Who's to blame? *Respirology*, *20*(3), 361–369. https://doi.org/10.1111/resp.12498

Gallo, A. M., Hadley, E. K., Angst, D. B., Knafl, K. A., & Smith, C. A. M. (2008). Children ' s Genetic Conditions. *Journal for Specialists in Pediatric Nursing*, *13*(1), 4–14. https://doi.org/10.1111/j.1744-6155.2008.00129.x

Gallop, K., Wild, D., Nixon, A., Verdian, L., & Cramer, J. A. (2009). Impact of Lennox-Gastaut Syndrome (LGS) on health-related quality of life (HRQL) of patients and caregivers: Literature review. *Seizure*, *18*(8), 554–558. https://doi.org/10.1016/j.seizure.2009.06.005

Glenn, A. D. (2015). Using online health communication to manage chronic sorrow: Mothers of children with rare diseases speak. *Journal of Pediatric Nursing*, *30*(1),

17–24. https://doi.org/10.1016/j.pedn.2014.09.013

Gliklich, R., & Leavy, M. (2011). Patient registries and rare diseases. *Applied Clinical Trials*, *20*(3), 1–5.

Graungaard, A. H., & Skov, L. (2007). Why do we need a diagnosis? A qualitative study of parents' experiences, coping and needs, when the newborn child is severely disabled. *Child: Care, Health and Development*, *33*(3), 296–307. https://doi.org/10.1111/j.1365-2214.2006.00666.x

Griggs, R. C., Batshaw, M., Dunkle, M., Gopal-Srivastava, R., Kaye, E., Krischer, J., … Merkel, P. A. (2009). Clinical research for Rare Disease: opportunities, challenges, and solutions. *Molecular Genetics and Metabolism*, *96*(1), 20–26. https://doi.org/10.1016/j.ymgme.2008.10.003

Grünewald, S. (2009). The clinical spectrum of phosphomannomutase 2 deficiency (CDG-Ia). *Biochimica et Biophysica Acta - Molecular Basis of Disease*, *1792*(9), 827–834. https://doi.org/10.1016/j.bbadis.2009.01.003

Grut, L., Kvam, M. H., & Lippestad, J. W. (2008). Rare disorders in Norway How the users experience the health services. Retrieved from http://www.sintef-norge.no/globalassets/upload/helse/levekar-og-tjenester/

Gundersen, T. (2011). "One wants to know what a chromosome is": The internet as a coping resource when adjusting to life parenting a child with a rare genetic disorder. *Sociology of Health and Illness*, *33*(1), 81–95. https://doi.org/10.1111/j.1467-9566.2010.01277.x

Havermans, T., Tack, J., Vertommen, A., Proesmans, M., & de Boeck, K. (2015). Breaking bad news, the diagnosis of cystic fibrosis in childhood. *Journal of Cystic Fibrosis*, *14*(4), 540–546. https://doi.org/10.1016/j.jcf.2014.12.005

Hennekam, R. C. M. (2011). Care for patients with ultra-rare disorders. *European Journal of Medical Genetics*, *54*(3), 220–224. https://doi.org/10.1016/j.ejmg.2010.12.001

Jaeken, J. (2003). Komrower Lecture. Congenital disorders of glycosylation (CDG): it's all in it! *Journal of Inherited Metabolic Disease*, *26*(2–3), 99–118. https://doi.org/10.1007/s10545-011-9299-3

Jaeken, J. (2011). Congenital disorders of glycosylation (CDG): It's (nearly) all in it!

Journal of Inherited Metabolic Disease, *34*(4), 853–858. https://doi.org/10.1007/s10545-011-9299-3

Jaeken, J., Lefeber, D., & Matthijs, G. (2015). Clinical utility gene card for: ALG6 defective congenital disorder of glycosylation. *European Journal of Human Genetics : EJHG*, *23*(2), 1–3. https://doi.org/10.1038/ejhg.2014.146

Jaeken, J., & Péanne, R. (2017). What is new in CDG? *Journal of Inherited Metabolic Disease*, 1–17. https://doi.org/10.1007/s10545-017-0050-6

Jaffe, A., Zurynski, Y., Beville, L., & Elliott, E. (2010). Call for a national plan for rare diseases. *Journal of Paediatrics and Child Health*, *46*(1–2), 2–4. https://doi.org/10.1111/j.1440-1754.2009.01608.x

Jensen, M. P., Brunklaus, A., Dorris, L., Zuberi, S. M., Knupp, K. G., Galer, B. S., & Gammaitoni, A. R. (2017). The humanistic and economic burden of Dravet syndrome on caregivers and families: Implications for future research. *Epilepsy and Behavior*, *70*, 104–109. https://doi.org/10.1016/j.yebeh.2017.02.003

Kao, B., Romero-Bosch, L., Plante, W., & Lobato, D. (2012). The experiences of Latino siblings of children with developmental disabilities. *Child: Care, Health and Development*, *38*(4), 545–552. https://doi.org/10.1111/j.1365-2214.2011.01266.x

Katz, S. (2002). When the child's illness is life threatening: impact on the parents. *Pediatric Nursing*, *28*(5), 453–463. Retrieved from http://search.ebscohost.com/login.aspx?direct=true&db=c8h&AN=2003046137&site=ehost-live

Kepreotes, E., Keatinge, D., & Stone, T. (2010). The experience of parenting children with chronic health conditions : a new reality. *Journal of Nursing and Healthcare of Chronic Illness*, *2*(1), 51–62. https://doi.org/10.1111/j.1752-9824.2010.01047.x

Kim, K. R., Lee, E., Namkoong, K., Lee, Y. M., Lee, J. S., & Kim, H. D. (2010). Caregiver's Burden and Quality of Life in Mitochondrial Disease. *Pediatric Neurology*, *42*(4), 271–276. https://doi.org/10.1016/j.pediatrneurol.2009.11.012

Knafl, K. A. (1998). Meeting the Challenges of Chronic Illness for Children and Families: Research and Future Directions. In M. Broome, K. Knafl, K. Pridham, & S. Feetham (Eds.), *Children and families in health and illness.* (pp. 236–245). Thousand Oaks:

Sage Publications, Inc.

Knafl, K. A., Darney, B. G., Gallo, A. M., & Angst, D. B. (2010). Parental perceptions of the outcome and meaning of normalization. *Research in Nursing and Health*, *33*(2), 87–98. https://doi.org/10.1002/nur.20367

Knight, A., & Senior, T. (2006). The common problem of rare disease in general practice. *Medical Journal of Australia*, *185*(2), 2–3. Retrieved from https://www.mja.com.au/system/files/issues/185_02_170706/kni10328_fm.pdf

Kumari, S. (2017). Nurturing values in disabled children : Role of psychology, *8*(5), 361–364.

Landfeldt, E., Lindgren, P., & Bell, C. F. (2014). The burden of Duchenne muscular dystrophy. *Neurology*, *83*, 529–536. https://doi.org/http://dx.doi.org/10.1212/WNL.0000000000000669

Lazarus, R. S., & Folkam, S. (1984). *Stress, Appraisal, and Coping*. New York: Springer.

Lipinski, S. E., Lipinski, M. J., Biesecker, L. G., & Biesecker, B. B. (2006). Uncertainty and perceived personal control among parents of children with rare chromosome conditions: The role of genetic counseling. *American Journal of Medical Genetics, Part C: Seminars in Medical Genetics*, *142*(4), 232–240. https://doi.org/10.1002/ajmg.c.30107

Malcolm, C., Gibson, F., Adams, S., Anderson, G., & Forbat, L. (2013). A relational understanding of sibling experiences of children with rare life-limiting conditions: Findings from a qualitative study. *Journal of Child Health Care : For Professionals Working with Children in the Hospital and Community*, *18*(3), 230–240. https://doi.org/10.1177/1367493513485825

Manor-Binyamini, I., & Abu-Ajaj, O. (2012). Coping of siblings of children with developmental disabilities in the Bedouin community. *Research in Developmental Disabilities*, *33*(3), 825–831. https://doi.org/10.1016/j.ridd.2011.11.016

Marklová, E., & Albahri, Z. (2007). Screening and diagnosis of congenital disorders of glycosylation. *Clinica Chimica Acta*, *385*(1–2), 6–20. https://doi.org/10.1016/j.cca.2007.07.002

Marquardt, T., & Denecke, J. (2003). Congenital disorders of glycosylation: review of

their molecular bases, clinical presentations and specific therapies. *European Journal of Pediatrics*, *162*(January), 359–379. https://doi.org/10.1007/s00431-002-1136-0

Marques-da-Silva, D., dos Reis Ferreira, V., Monticelli, M., Janeiro, P., Videira, P. A., Witters, P., … Cassiman, D. (2017). Liver involvement in congenital disorders of glycosylation (CDG). A systematic review of the literature. *Journal of Inherited Metabolic Disease*, *40*(2), 195–207. https://doi.org/10.1007/s10545-016-0012-4

Marques-da-Silva, D., Francisco, R., Webster, D., dos Reis Ferreira, V., Jaeken, J., & Pulinilkunnil, T. (2017). Cardiac complications of congenital disorders of glycosylation (CDG): a systematic review of the literature. *Journal of Inherited Metabolic Disease*. https://doi.org/10.1007/s10545-017-0066-y

Mathiesen, A. M., Frost, C. J., Dent, K. M., & Feldkamp, M. L. (2012). Parental needs among children with birth defects: Defining a parent-to-parent support network. *Journal of Genetic Counseling*, *21*(6), 862–872. https://doi.org/10.1007/s10897-012-9518-6

Mazaheri, M. M., Rae-Seebach, R. D., Preston, H. E., Schmidt, M., Kountz-Edwards, S., Field, N., … Packman, W. (2013). The impact of Prader-Willi syndrome on the family's quality of life and caregiving, and the unaffected siblings' psychosocial adjustment. *Journal of Intellectual Disability Research*, *57*(9), 861–873. https://doi.org/10.1111/j.1365-2788.2012.01634.x

McGill Smith, P. (2014). You are not alone: For parents when they learn their child has a disability. *NICHCY News Digest*, *20*(3), 2–6. https://doi.org/1.800.695.0285

Michalík, J. (2014). The Quality of Life of Caregivers who Care for a Child with a Rare Disease – Perception of Changes as a Result of Care in the Czech Republic. *Procedia - Social and Behavioral Sciences*, *112*(Iceepsy 2013), 1149–1159. https://doi.org/10.1016/j.sbspro.2014.01.1279

Monin, M.-L., Mignot, C., De Lonlay, P., Héron, B., Masurel, A., Mathieu-Dramard, M., … Héron, D. (2014). 29 French adult patients with PMM2-congenital disorder of glycosylation: outcome of the classical pediatric phenotype and depiction of a late-onset phenotype. *Orphanet Journal of Rare Diseases*, *9*, 207. https://doi.org/10.1186/s13023-014-0207-4

Monticelli, M., Ferro, T., dos Reis Ferreira, V., Jaeken, J., & Videira, P. A. (2016). Immunological aspects of congenital disorders of glycosylation (CDG): a review. *Journal of Inherited Metabolic Disease*, *3*(10), 3323–31. https://doi.org/10.1007/s12192-010-0223-9

Morelle, W., Potelle, S., Witters, P., Wong, S., Climer, L., Lupashin, V., … Foulquier, F. (2017). Galactose supplementation in patients with TMEM165-CDG rescues the glycosylation defects. *Journal of Clinical Endocrinology and Metabolism*, *102*(4), 1375–1386. https://doi.org/10.1210/jc.2016-3443

Moreno García, I., Antequera Jurado, R., Aires González, M. del M., Colado Huertas, S., & Díaz Rubiales, S. (2008). Demanda de apoyo psicosocial en cuidadores de niños con enfermedades de baja prevalencia. *Apuntes de Psicología*, *26*(2), 349–360. Retrieved from http://search.proquest.com/docview/622135982?accountid=14744%5Cnhttp://fama.us.es/search*spi/i?SEARCH=02133334%5Cnhttp://pibserver.us.es/gtb/usuario_acceso.php?centro=$USEG&centro=$USEG&d=1

Nolbris, M., Enskär, K., & Hellström, A. L. (2007). Experience of siblings of children treated for cancer. *European Journal of Oncology Nursing*, *11*(2), 106–112. https://doi.org/10.1016/j.ejon.2006.10.002

O'Brien, I., Duffy, A., & Nicholl, H. (2009). Impact of childhood chronic illnesses on siblings: a literature review. *British Journal of Nursing*, *18*(22).

Paster, A., Brandwein, D., & Walsh, J. (2009). A comparison of coping strategies used by parents of children with disabilities and parents of children without disabilities. *Research in Developmental Disabilities*, *30*(6), 1337–1342. https://doi.org/10.1016/j.ridd.2009.05.010

Pelentsov, L. J., Fielder, A. L., & Esterman, A. J. (2015). The supportive care needs of parents with a child with a rare disease: A qualitative descriptive study. *Disability and Health Journal*, *8*(4), 475–491. https://doi.org/https://doi.org/10.1016/j.pedn.2015.10.022

Pelentsov, L. J., Fielder, A. L., Laws, T. A., & Esterman, A. J. (2016). The supportive care needs of parents with a child with a rare disease: results of an online survey. *Disability and Health Journal*, *8*(4), 475–491.

https://doi.org/10.1016/j.dhjo.2015.03.009

Pelentsov, L. J., Laws, T. A., & Esterman, A. J. (2015). The supportive care needs of parents caring for a child with a rare disease: A scoping review. *Disability and Health Journal*, *8*(4), 475–491. https://doi.org/https://doi.org/10.1016/j.dhjo.2015.03.009

Picci, R. L., Oliva, F., Trivelli, F., Carezana, C., Zuffranieri, M., Ostacoli, L., … Lala, R. (2015). Emotional Burden and Coping Strategies of Parents of Children with Rare Diseases. *Journal of Child and Family Studies*, *24*(2), 514–522. https://doi.org/10.1007/s10826-013-9864-5

Read, C. Y. (2003). The demands of biochemical genetic disorders: A survey of mothers of children with mitochondrial disease or phenylketonuria. *Journal of Pediatric Nursing*, *18*(3), 181–186. https://doi.org/10.1053/jpdn.2003.36

Read, J., Kinali, M., Muntoni, F., Weaver, T., & Garralda, M. E. (2011). Siblings of young people with Duchenne muscular dystrophy - A qualitative study of impact and coping. *European Journal of Paediatric Neurology*, *15*(1), 21–28. https://doi.org/10.1016/j.ejpn.2010.07.006

Roper, S. O., Allred, D. W., Mandleco, B., Freeborn, D., & Dyches, T. (2014). Caregiver burden and sibling relationships in families raising children with disabilities and typically developing children. *Families, Systems & Health*, *32*(2), 241–6. https://doi.org/10.1037/fsh0000047

Santos, M. C. dos, & Barros, L. (2015). Intervenção com pais de crianças com doença crónica. In A. I. Pereira, A. R. Goes, & L. Barros (Eds.), *Promoção da Parentalidade Positiva : Intervenções psicológicas com pais de crianças e adolescentes*. Coisas de Ler.

Santos, M. C. dos, Pires, A. F., Soares, K., & Barros, L. (2017). Family experience with osteogenesis imperfecta type 1: the most distressing situations. *Disability and Rehabilitation*, 1–7. https://doi.org/http://dx.doi.org/10.1080/09638288.2017.1334236

Schachter, H., & Freeze, H. H. (2009). Glycosylation diseases: Quo vadis? *Biochimica et Biophysica Acta - Molecular Basis of Disease*, *1792*(9), 925–930. https://doi.org/10.1016/j.bbadis.2008.11.002

Schieppati, A., Henter, J. I., Daina, E., & Aperia, A. (2008). Why rare diseases are an important medical and social issue. *The Lancet*, *371*(9629), 2039–2041. https://doi.org/10.1016/S0140-6736(08)60872-7

Senger, B. A., Ward, L. D., Barbosa-Leiker, C., & Bindler, R. C. (2016). Stress and coping of parents caring for a child with mitochondrial disease. *Applied Nursing Research*, *29*, 195–201. https://doi.org/10.1016/j.apnr.2015.03.010

Sharpe, D., & Rossiter, L. (2002). Siblings of Children With a Chronic Illness: A Meta-Analysis. *Journal of Pediatric Psychology*, *27*(8), 699–710. https://doi.org/10.1093/jpepsy/27.8.699

Shilling, V., Morris, C., Thompson-Coon, J., Ukoumunne, O., Rogers, M., & Logan, S. (2013). Peer support for parents of children with chronic disabling conditions: A systematic review of quantitative and qualitative studies. *Developmental Medicine and Child Neurology*, *55*(7), 602–609. https://doi.org/10.1111/dmcn.12091

Siddiq, S., Wilson, B. J., Graham, I. D., Lamoureux, M., Khangura, S. D., Tingley, K., … Potter, B. K. (2016). Experiences of caregivers of children with inherited metabolic diseases: a qualitative study. *Orphanet Journal of Rare Diseases*, 1–11. https://doi.org/10.1186/s13023-016-0548-2

Sparks, S. E., & Krasnewich, D. M. (2005). PMM2-CDG (CDG-Ia). Retrieved March 20, 2017, from https://www.ncbi.nlm.nih.gov/books/NBK1110/

Van Scherpenzeel, M., Willems, E., & Lefeber, D. J. (2016). Clinical diagnostics and therapy monitoring in the congenital disorders of glycosylation. *Glycoconjugate Journal*, *33*(3), 345–358. https://doi.org/10.1007/s10719-015-9639-x

Wallander, J. L., & Varni, J. W. (1998). Effects of pediatric chronic physical disorders on child and family adjustment. *Journal of Child Psychology and Psychiatry, and Allied Disciplines*, *39*(1), 29–46. https://doi.org/10.1111/1469-7610.00302

Weng, H. J., Niu, D. M., Turale, S., Tsao, L. I., Shih, F. J., Yamamoto-Mitani, N., … Shih, F. J. (2012). Family caregiver distress with children having rare genetic disorders: A qualitative study involving Russell-Silver Syndrome in Taiwan. *Journal of Clinical Nursing*, *21*(1–2), 160–169. https://doi.org/10.1111/j.1365-2702.2010.03583.x

Williams, J. K., Skirton, H., Paulsen, J. S., Tripp-Reimer, T., Jarmon, L., McGonigal Kenney, M., … Honeyford, J. (2009). The emotional experiences of family carers in Huntington disease. *Journal of Advanced Nursing*, *65*(4), 789–798. https://doi.org/10.1111/j.1365-2648.2008.04946.x

Wolthuis, D. F. G. J., Janssen, M. C., Cassiman, D., Lefeber, D. J., & Morava-Kozicz, E. (2014). Defining the phenotype and diagnostic considerations in adults with congenital disorders of N-linked glycosylation. *Expert Review of Molecular Diagnostics*, *14*(2), 217–224. https://doi.org/10.1586/14737159.2014.890052

Wong, S. Y.-W., Gadomski, T., van Scherpenzeel, M., Honzik, T., Hansikova, H., Holmefjord, K. S. B., … Morava, E. (2017). Oral D-galactose supplementation in PGM1-CDG. *Genetics in Medicine : Official Journal of the American College of Medical Genetics*, *0*(November 2016), 1–10. https://doi.org/10.1038/gim.2017.41

Woodgate, R. L. (2006). Siblings' Experiences With Childhood Cancer: A Different Way of Being in the Family. *Cancer Nursing*, *29*(5), 406–414.

Zurynski, Y., Deverell, M., Dalkeith, T., Johnson, S., Christodoulou, J., Leonard, H., & Elliott, E. J. (2017). Australian children living with rare diseases: experiences of diagnosis and perceived consequences of diagnostic delays. *Orphanet Journal of Rare Diseases*, *12*(1), 68. https://doi.org/10.1186/s13023-017-0622-4

Zurynski, Y., Frith, K., Leonard, H., & Elliott, E. (2008). Rare childhood diseases: how should we respond? *Archives of Disease in Childhood*, *93*(12), 1071–4. https://doi.org/10.1136/adc.2007.134940

APPENDIX

APPENDIX A – Letter of collaboration with the Portuguese Association of Congenital Disorders of Glycosylation and other Rare Metabolic Diseases (APCDG-DMR).

Associação Portuguesa CDG (APCDG)

Lisboa, 10 de Feveiro de 2017.

DECLARAÇÃO

Atendendo ao interesse e relevância dos dados a recolher, a Associação Portuguesa de CDG (APCDG) é parceira no estudo " *The subjective experience of the families of a patient with a Congenital Disorders of Gíycosylation: identifying needs and sources of support*" a realizar pela estudante de Mestrado Integrado em Psicologia Carolina Cardão e orientado pela Professora Doutora Luisa Barros, da FPUL.

A APCDG, fundou e coordena a única rede de investigação internacional de associações de doentes CDG e profissionais de saúde denominada CDG & Allies PPAIN (para mais informação visite AQUI). Sendo a área de investigação da Professora Doutora Luísa Barros, da FPUL de grande interesse para o conjunto de patologias por nós representadas, a Pf Dr Barros uniu-se à CDG & Allies PPAIN e é coordenadora de um dos nossos Working Groups denominado Work Package 7- CDG psychology and educational research (pode consultar AQUI). A nossa parceria permitirá aprender mais sobre o impacto emocional do diagnóstico desta patologias junto das famílias e visa reunir estratégias usadas pelas familias para superar os vários desafios enfrentados.

A Associação Portuguesa de CDG compromete-se a divulgar o estudo na sua página e redes sociais e a identificar famílias de pessoas com CDG que estejam disponíveis para participar no referido estudo. No caso de haver uma primeira manifestação de interesse em participar nesse estudo e autorização para fornecer o contacto à equipa de investigação, a Associação comunica essa informação. Os membros da equipa enviarão então um email com informação mais detalhada sobre o estudo e com o protocolo de consentimento informado ao potencial participante. Os potenciais participantes, interessados em prosseguir com a sua participação no estudo, devem enviar uma cópia assinada do consentimento informado, em formato digitalizado ou por correio,

para a responsável pelo estudo. Qualquer entrevista ou outra recolha de dados só poderá ser realizada depois de o consentimento informado estar na posse dos investigadores.

Com os melhores cumprimentos,

Vanessa Miriam dos Reis Ferreira, PhD MBA CDG & Allies PPAIN founder and coordinator APCDG founder

APPENDIX B – Letter sent to participants with detailed study aims and conditions.

Dear Mr/Mrs (name of the participant)

We are writing to you to invite you and your family to participate in a study about the experiences of families with a patient with CDG, this study integrates a larger project in the context of a partnership between Psychology Faculty of the University of Lisboa, Portugal and the Portuguese Association for CDG (APCDG). We are aiming to contribute to the understanding of the main needs and sources of support that families with a relative with Congenital Disorder of Glycosylsation (CDG) may require. Recognizing that the persons who live daily with a CDG patient are an important and authorized source of information, we intend to conduct interviews with the main caretakers and other family members (siblings, grandparents), to understand their perspectives about: 1) What it is like to live with a CDG patient; 2) What are the main challenges and difficulties of living with a CDG patient; 3) What are the main sources of support and the coping strategies they consider more useful. The results will be disseminated among families, associations and professionals working with CDG in different countries taking advantage of the existing international research network CDG&Allies - Professionals and Patient Associations International Network.

As families are scattered in different countries and regions, interviews will be conducted by a **Skype call**. These interviews will last between **20 and 45 minutes**, in a **singular** session.

Please acknowledge that:

- Your participation is an **important contribution** to our **knowledge and understanding** about life with a CDG patient and this knowledge will be disseminated among the **academic community** and the **healthcare professionals**, in order to help develop more adequate and effective interventions as well as support provisions.

- Your participation is **completely voluntary** and you **can interrupt the interview or stop your collaboration with this study at any moment and for any**

reason, knowing that your decision will not have any kind of consequences for you and your family.

- The interview will be **tapped** and the records will only be **used for this study** and destroyed at the end of the study, to guarantee the **confidentiality** of the information you shared with us.

- All the information regarding your and of your **family identity** will be treated as strictly **confidential** and will not be shared with other persons then the authors of this study.

- The **main results of this study**, considering the global analysis of all individual interviews, will be **made available** to you.

If you agree to participate in the study, please send an email to (mail of APCDG-DMR collaborator), allowing APCDG to give us access to your contact information. You will then be **contacted, by email**, to arrange a **date and hour** suitable for your participation.

In your answer, please provide information about the age of the CGD patient and about which family members are available to participate in an interview (Mother, father, sibling, other relative living with the patient).

Your collaboration is very important!

APPENDIX C – Informed consent sent to participants.

Informed Consent

This study aims to contribute to a better understanding of the main needs and sources of support that families with a relative with Congenital Disorder of Glycosylation (CDG) may require. The study will be conducted in the context of a partnership between the Portuguese Association for CDG and other Rare Metabolic Diseases (APCDG-DMR) and the University of Lisbon and the authors are Luísa Barros, PhD and Carolina Cardão, MA student. Recognizing that the persons who live daily with a CDG patient are an important and authorized source of information, an interview will be conducted to listen to the different family members' perspective about what it is like to live with a CDG patient, what are their main challenges and difficulties, as well as their main sources of support and the coping strategies they consider more useful.

As families are scattered in different countries and regions, interviews will be conducted by a Skype call. These interviews will last between 30 minutes and 1 hour, in one only session, and will be made in the native language of the participants.

If you agree to participate in the study, please acknowledge that:

- Your participation is an important contribution to our knowledge and understanding about life with a CDG patient and this knowledge will be disseminated to the academic community and the healthcare professionals in order to help develop more adequate and effective interventions and support provisions.
- Your participation is completely voluntary and you can interrupt the interview or stop your collaboration with this study at any moment and for any reason, knowing that your decision will not have any kind of consequences for you and your family.
- The interview will be tapped and the records will only be used for this study and destroyed at the end of it, to guarantee the confidentiality of the information you shared with us.

- This study is not anonymous, but all the information regarding you and of your family identity will be anonymized and will be treated as strictly confidential, and will not be shared with other persons than the authors.
- The main results of this study, considering the global analysis of all individual interviews, will be made available through you, in the language chosen by you.

For any further queries, please contact Carolina Cardão to ccardao@campus.ul.pt.

I, _____ declare that I am aware of the aims of the investigation and of the procedures needed for my participation on it, and for that I accept to participate.

(Complete Name) _____

(Date) _____

(Signature) _____

APPENDIX D – Script of the semi-structured interviews

Semi-structured Interview - Script

Presentation

- Thank the participants for the availability to help us in our study;
- Explain briefly the main aims of the study and what we pretend with the interview: the main aim of this interview is to collect information from people that directly experience how living with a CDG patient, so we can provide health professionals and the people in general a better understanding of the challenges of these families, the resources they have available, the coping strategies they use to deal with the daily challenges and the overall impact of CDG in the family and in each of the members of it;
- Inform that the participation is voluntary and if they do not feel comfortable with some questions they have the right not to answer or even to interrupt the interview;
- Ask for the authorization to record (sound and/or video) the interview, and make clear that the data collected is confidential, which means that only the team members will have access to it, that all care will be taken so that the participants or families ca not be identified and that all the records and personal information will be destroyed at the end of the study.

Proposal for the structure of the script of the interview

This is a semi-structured interview that will pursue according to the answers provided by the participant, giving space for each participant to talk freely about what is important for him/her. The topics will all be covered as long as the participant is willing to answer. The questions provided are presented as examples, but the interviewer will adapt her language to the discourse and specific language of the respondent and will allow space for the participant to introduce a new topic that he/she considers relevant.

- **Opening sentence** (We will ask you some questions so that you can help us understand how is it to live with a child/sibling/other family member with CDG). Some questions may be unnecessary or inadequate for some participants, according to what they are reporting.

- **Knowledge of the disease**

Topics to explore	Examples of questions
<u>General knowledge of the identity of the disease:</u> Explore the participants' knowledge of the disease; how do they define CDG; what are the main features and symptoms of the disease; where did they get the information from; what would they like to know more about the disease.	Can you explain a bit the main characteristics of CDG? (features and symptoms) How would you explain what is CDG syndrome to someone that doesn't know anything about it? Where did you get all the information you have about CDG? (patient group, doctor, specialist, internet, books) Is there anything else you would like to know about CDG that you don't know now yet? Did this lack of information cause you some worry? (what would they like to know, which feelings emerge from not knowing everything). If you could talk with the person who knows the most about CDG, what would you like to ask? What do you know about the impact of the disease on the individual and the family? (how do they know this, by experience, knowing other CDG families, by reading on the internet/books…)
<u>Knowledge about causes of the disease:</u> Concerning the determinants/ causes of CDG, explore the knowledge that the family members have and how did they reach this level of information.	Do you know why CDG happens? What can cause/ contribute to the occurrence of CDG? Have you received information or thought about why your child (sibling, etc) has CDG? (which kind of information did they received, from who/where; are they concerned about this?)
<u>Moment of diagnosis:</u> Explore what were the events that lead to the diagnosis of CDG (family concerns that something was wrong with the child, physicians' identification of warning signs).	Can you tell me about when and how was the diagnosis made? There were symptoms that made you think there was something seriously wrong with your child? Or was it the doctor that identified the first signs? (did any signs and/or symptoms made the family worry that something was different with the child, did they consider the possibility of any specific disease).

Explore thoughts, emotions, and memories of this period of time around the diagnosis (before, at the moment and right after); how did the family cope with the new information; what did they do; who was/were the most important support at that moment.	Who made the diagnosis of CDG? How did you receive the information that your child had CDG? (who told them, how was it explained, first questions made to themselves) Did you immediately understand that CDG was a chronic and rare condition? How long did you/your family had to wait for a final diagnosis after the first worries and doubts about the possibility of a serious disease? How many doctors did you/your family see before the final diagnosis? Was your child been misdiagnosed before the CDG diagnosis? What was the misdiagnosis made? Does your child have other health conditions other than CDG? Did these other health conditions interfere with the diagnosis of CDG? Did you consult a specialist on CDG? How long did it take to find him? If not, did you try to get one? What feelings raised from the search time it took to get a CDG specialist? What were the main feelings upon the diagnosis? (feelings of depression, anxiety; less interaction with family/friends, isolation) When you think about that moment, what memories come immediately to your mind? Who did support you by that time? What do you remember being more useful during that period?

- **Living with CDG**

Topics to explore	**Examples of questions**
<u>Symptoms and consequences of the disease:</u>	We would like to know how CDG affects your child's (relative) daily life. How is it to live with a CDG patient? What are the main difficulties?

Explore the symptoms experienced in the present and what the participants consider as the main consequences of the disease for the child. Explore how the disease affects the family, which are the consequences/impact for the interviewed and for other family members; how did the disease change and currently affects the family routines and daily living (explore the perspectives of each member of the family interviewed). Explore the existence of positive aspects about living with a child with CDG; what did change in the family that can be considered positive; which benefits does each member of the family considers that they achieved from the daily life with CDG.	What are the main (heavier, dominant) symptoms of CDG for (name of patient)? What can you do as a parent/other family member to relieve these symptoms? Who is responsible for these tasks? (who is the principal care figure, who does what, do the several family members participate in the patients' care) When you think about your child's health and everyday life, what are the main consequences of having CDG for him? (biggest limitations now and in the future) How is it for you to live and deal with CDG in everyday life? Does having a child/relative with CDG changed your family's life? In what ways? (routines of the family, financial consequences, need to travel long distance, how are all these demands managed) Do you need to travel long distances to attend medical care centers? What have been the financial consequences after the CDG diagnosis? How do living with a CDG relative affected you as a parent (brother, grandparent, etc)? Often people that deal with a chronically ill family member report important positive experiences, learning, emotions, and support. Can you tell us about some form of positive impact /meaning of living with your relative with CDG?
<u>Transition from pediatrics to adult</u> <u>(only when the patient is an adult)</u> Explore the main differences about dealing with a child and an adult with CDG; what did change and in which ways. Explore what did change in the relationship with the health care	Since your son/daughter/sibling is an adult, what did change in his/her care/treatment/ health care? Are there important differences in the support and relationship with the healthcare team? How was this transition made? What are the biggest differences between having a child with CDG and an adult with CDG?

professionals; how is the relationship managed now. (Only applicable when the family interviewed has a relative with CDG that is already an adult).	
<u>Difficulties and concerns, coping strategies and social support:</u> Explore the main difficulties in managing the disease and its challenges and barriers of living with a child with CDG; how does the family deal with these difficulties; which strategies do they use to cope with the CDG demands. Explore situations that were most disturbing and try to understand what does make them so memorable to the interviewed. Explore actual concerns and about the future. Explore the social support given to the family.	What are the main difficulties faced in your daily life, concerning the care and demands of CDG? How does your family deal with these difficulties? And you? (explore how the interviewed sees the way of dealing of the family and how he/she perceives his/her own way of dealing with the difficulties) What kind of strategies do you use to overcome that difficulties? Where did you learn them? Can you recall some situations that were particularly difficult/ disturbing? What did you feel in those situations? And how did they end? What have been the more useful strategies you have learned to use in difficult situations? Nowadays, what are your most important concerns regarding the patient? Why? How are you dealing with it? Can you tell me a little about the different feelings about caring you're your relative with CDG? What kind of feelings you experience more often and/or more intensively? (depression, anxiety, ...) Who is your main support? (family, friends, community, patient groups, health professionals) What kind of support is the most useful for you? How does it help you? Do you feel you would benefit from other kind of support? Like what? Does your child, you and/or other family members have or had some form of

	psychological support? Since when? Did you search for it or was it offered to you? Was/Is it helpful? In what way? If you/your child are/is not being receiving psychological support, do you feel it would help you? In which ways?
Treatments and therapies Explore the treatments and therapies used by the child, and how are they managed between the family members.	What are the treatments that your child needs to receive daily or regularly (for what? how is the administration?) Who are responsible for the treatments? (family member, health care professionals, etc.) Do you have to go to a special health care center so your child can receive treatment?
Relationship with the health care professionals Explore the relationship with the health care professionals; how is the communication between them; what would they like to change or improve.	Who are the health professionals that you felt as more supportive/helpful? How would you describe your relationship with the health professionals responsible for the care of your child? Is the relationship now different from the beginning? Why? What did change? Would you like something in this relationship to change? In what way? What would you like the health professionals to know about your experience of a parent/sibling/grandparent of a child with CDG? Did you had to explain what is CDG to any health professionals? (when and to whom)

- **Evolution of the disease**

Topics to explore	Examples of questions
Future perspectives Explore the expectations of the participant about the evolution of the CDG and the changes in needs and care challenges.	Now I would like you to tell me a little about what do you think about the near future. What are your main concerns and worries?

As an end, ask to the family "If you had been asked to talk with a family that had just found out that their child has CDG, what would you like to say to them that you think could be helpful?".